



Panacea Biotec

Innovation in support of life

IN THE UNITED STATES PATENTS AND TRADEMARKS OFFICE

Application of: JAIN, Rajesh

Serial No.: 10/089,020

Filed On: Mar 27, 2003

For: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

Group: 1616

Examiner: Pryor Alton Nathaniel

Docket No.: U 013943-5

Commissioner of Patents & Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, RAJESH JAIN, Ph.D, Joint Managing Director of Panacea Biotec Limited, hereby declare that:

1. I am one of the applicants in the aforesaid application. My C.V. is attached herewith.
2. I would like to bring to the notice of the learned examiner - (i) why there exists a need for a once-a-day composition of nimesulide and why there is a market for an effective and safe controlled-release dosage form of nimesulide globally, that is prepared in a easy and cost effective manner (ii) encouraging *in vivo* efficacy results obtained from the bilayered controlled-release dosage form of nimesulide of the present invention and (iii) the broad acceptance and commercial success of this novel dosage form in the domestic market, in India where it is being sold.

3. Nimesulide (4-nitro-2-phenoxy-methan-sulfanilide) is a potent non steroidal anti-inflammatory drug, presently used in the treatment of painful inflammatory conditions, which also possesses antipyretic activity. Compared to the other non steroidal anti-inflammatory drugs, Nimesulide has a better therapeutic ratio, low acute gastrotoxicity and generally good tolerability with no reported cardiovascular adverse effects. Nimesulide is chemically different from other drugs in this class because of the presence of sulfonamide moiety. Nimesulide has exhibited potency similar to or greater than indomethacin, diclofenac, piroxicam and ibuprofen in animal models. Many published articles report that nimesulide is an effective NSAID with relatively favorable safety profile for the treatment of osteoarthritis and non-rheumatoid musculoskeletal conditions¹. Nimesulide is different from Naproxen, nimesulide being a selective Cox-2 inhibitor, which makes it more tolerable and safe having reduced to no gastro-intestinal side effects, while Naproxen is a non-selective Cox inhibitor, its acts on both Cox-1 and Cox-2 receptors and thus leads to gastro-intestinal toxicity like ulceration, bleeding, which makes it unacceptable. Safety profile of nimesulide has been demonstrated by many published articles which are enclosed herewith for your kind perusal. Brief on the same is given below:

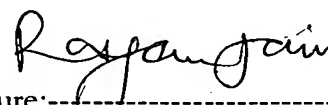
- (i) Denis Riendau et al; discloses the comparative study of COX-1 inhibitory properties of NSAIDs and selective COX-2 inhibitors. It reveals that the selective COX-2 inhibitors possess anti-inflammatory effects with an improved gastro-intestinal tolerability compared with conventional NSAIDs affecting both COX-1 and COX-2².
- (ii) Shah, A.A. et al; reveals that nimesulide has preferential selectivity for COX-2 over COX-1 *in-vivo* as full therapeutic doses and induces less gastrointestinal damages than that seen with naproxen in the short term³.
- (iii) Sheikh Arshad Saeed et al reported the anti-ischemic effect of nimesulide. In this study, it has been demonstrated that the nimesulide has significant improvement in the coronary perfusion rate which strongly suggest that coronary vasodilation occurs through endothelial dependant NO formation. There is evidence that COX-2 may be a source of oxygen radical itself and therefore, inhibition of this enzyme activity by nimesulide may reduce oxidative stress⁴.

- (iv) It has been further reviewed by Rainsford K.D. that the nimesulide has relatively low occurrence of gastro-intestinal side effects which is related to its low propensity to inhibit the physiologically important COX-1 in the GI mucosa and important physiochemical properties as well as inhibiting of mast cell derived histamine and acid secretion in the stomach. In contrast with coxib, nimesulide has not been found to have appreciable cardiovascular toxicity⁵.
4. At the time of development of this invention, nimesulide was available as oral immediate release dosage form to be administered up to 100 to 200 mg twice daily. I realized that for treatment of chronic diseases like arthritis the twice-daily dosing regimen is quite difficult to comply with. There was an impending need to develop a once-a-day composition to significantly increase the dosing convenience and patient compliance. There was also a need to develop a composition which will provide some part of the drug, nimesulide, as an immediate release pulse and release the remaining part of the drug as a constant release for extended period of time, thus providing a better efficacy in treatment of NSAID indicated disorders. Prior arts had suggested methods which were difficult to manufacture and were not cost effective, hence there was a need to develop the formulation in a very simple and cost effective manner.
5. This lead to the development of the once-a-day controlled-release tablet composition consisting of a single unit fast release layer and a single unit extended release layer (essentially bilayered tablet) comprising nimesulide as an active agent in both the layers, extended release layer further comprising rate controlling material as claimed. Surprisingly this formulation has an increased residence time in the desired site of absorption such as stomach and proximal part of small intestine, which makes it very advantageous over all prior arts particularly in terms of providing a better absorption of nimesulide and thus its efficacy. The said dosage form of nimesulide eliminates the absorption of nimesulide from distal part of small intestine and large intestine which lead to the loss of bioavailability. This rendered a novel feature to this invention.
6. A similar controlled-release once-a-day composition of nimesulide as described in our present invention in Example 10, has been studied *in vivo* against conventional

nimesulide dosage form i.e. Aulin 100mg. Details on the test that were conducted and the results obtained have been discussed in Annexure-1

7. The said composition of nimesulide was also tested *in vivo* against other NSAIDs (Diclofenac- SR 100 mg) to show comparative efficacy and safety and was found to be very comparable. Efficacy and safety data of Nimesulide Extended Release Tablet 200mg have been demonstrated in Annexure-2
8. I believe that the said composition of nimesulide has broader acceptance and success in the market place. Herein applicant provides you information in Annexure-3 (at best available to me) about-
 - (i) Total population for osteoarthritis patient globally
 - (ii) Available treatment for osteoarthritis, an inflammation disorder
 - (iii) Features of the claimed invention which render the composition as claimed to be highly effective and safe
 - (iv) Sales data of claimed product
9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this 20th day of April, 2009


Signature:-----
(RAJESH JAIN, Ph.D)

ANNEXTURE- 1

Two pivotal studies were conducted to characterize the pharmacokinetics of Nimesulide ER 200 mg tablets. The studies consisted of a (i) single-dose 3-arm fasting/fed study and a (ii) multiple-dose steady-state study

(1) Relative bioavailability of Nimesulide Extended Release Tablets 200 mg under fasting and Fed condition [Single-dose 3-arm fasting/fed study]

A randomized, open label, three-treatment, three-period, three-sequence, single dose, crossover, comparative bioavailability study, to assess the relative bioavailability of Nimesulide Extended Release (ER) Tablet 200 mg of Panacea Biotec Limited, India, Willgo[®] (under fasting and fed conditions) (similar in composition to that given in our present invention in Example 10) with Aulin[®] (Nimesulide 100 mg) Tablets of CSC Pharmaceuticals, Austria (under fasting condition) was carried out in healthy human adult male subjects.

A total of 36 healthy, adult male subjects aged between 18 - 50 years, having a body mass index (BMI) between 18 and 25 were enrolled for the study and housed for at least 37 hours. The study was conducted in three periods. In each period, subjects were dosed with one of the 3 study treatments: Treatment A: One tablet of Nimesulide ER 200 mg under fasting conditions, Treatment B: One tablet of Nimesulide ER 200 mg under fed conditions, Treatment C: Two tablets of Aulin[®] (Nimesulide 100 mg) under fasting conditions.

Sampling was done up to 24.0 hours such that the plasma concentration could be measured for adequately profiling the pharmacokinetics of the product. Study periods were separated by a washout period of 7 days for complete elimination of the product substance.

Summary of Pharmacokinetic data for Nimesulide ER 200 mg Tablet (Single dose Study)
Table 1

<i>Parameters</i>	<i>Single Dose study</i>		
	<i>Test (Fasting)</i>	<i>Test (Fed)</i>	<i>Reference (Fasting)</i>
AUC _{0-t} (µg.h/ml)	48.6004	93.6634	98.7289
AUC _{0-∞} (µg.h/ml)	51.0648	98.7918	102.9535
C _{max} (µg/ml)	5.6954	10.7552	12.9410
T _{max} (h)	2.98	5.12	2.38
t _{1/2} (h)	4.04	4.15	3.97
K _{el} (h) ⁻¹	0.1870	0.1837	0.1947
AUC _{0-t} / AUC _{0-∞}	0.9565	0.9556	0.9685

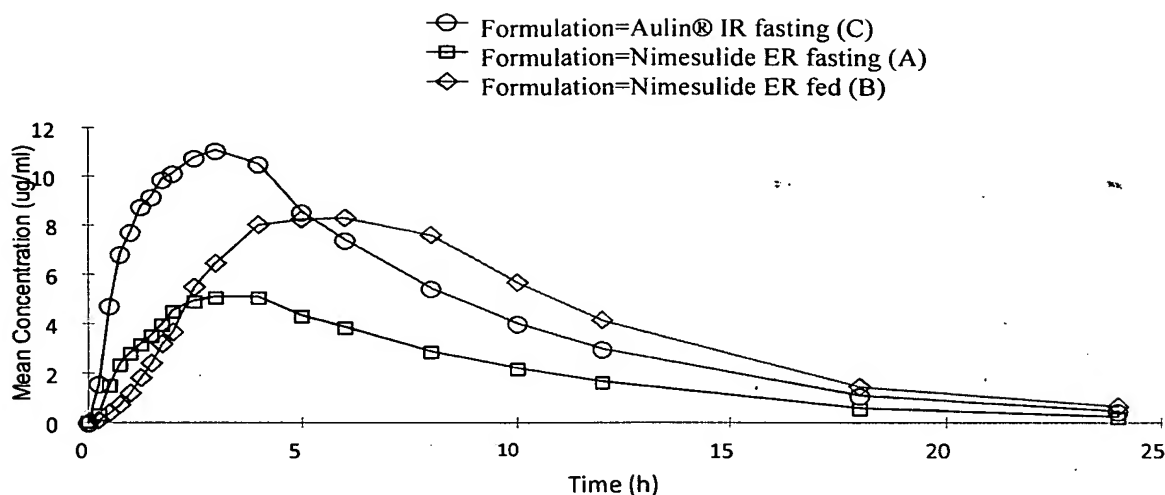


Fig. 1: Linear Plot of Mean Plasma Nimesulide Concentrations versus Time Profiles in Healthy Human Adult Male Subjects

Conclusion: As seen in Figure 1 food significantly increases the absorption of nimesulide from the extended release composition of the present invention and is bioequivalent to Aulin. Both test and reference formulations were found to be well tolerated in this study.

(2) A randomized, open label, two- treatment, two-period, two-sequence, multiple-dose, crossover, relative bioavailability study of Nimesulide Extended Release Tablets 200 mg Willgo® [Multiple-dose steady-state study].

A randomized, open label, two-treatment, two-period, two-sequence, multiple-dose, crossover, relative bioavailability study of Nimesulide Extended Release Tablet 200 mg of Panacea Biotec Limited, India with Aulin® (Nimesulide 100 mg) tablets (administered twice daily) of CSC Pharmaceuticals Austria, was conducted in healthy human adult male subjects, under fed condition.

A total of 36 healthy, adult male subjects of either sex aged between 18-50 years (inclusive) having a body mass index (BMI) between 18 and 25 were enrolled for the study. The subjects were dosed as determined by the randomization schedule.

(ANNEXTURE- 1 Contd.....)

There was a washout period of 8 days following administration of test product and 7½ days following administration of reference products between the dosings.

Summary of Pharmacokinetic data for Nimesulide ER 200 mg Tablet (Multiple dose Study)

Table 2

<i>Parameters</i>	<i>Multiple Dose study under fed condition</i>	
	<i>Test - A</i>	<i>Reference - B</i>
C_{min} (µg/ml)	0.5948	1.6482
C_{avg} (µg/ml)	4.0494	4.5142
C_{max} (µg/ml)	11.0428	8.5409
$AUC_{0-\tau_{ss}}$ (µg.h/ml)	97.1846	108.3398
%PTF	278.64	165.32
Swing	3424.78	685.88

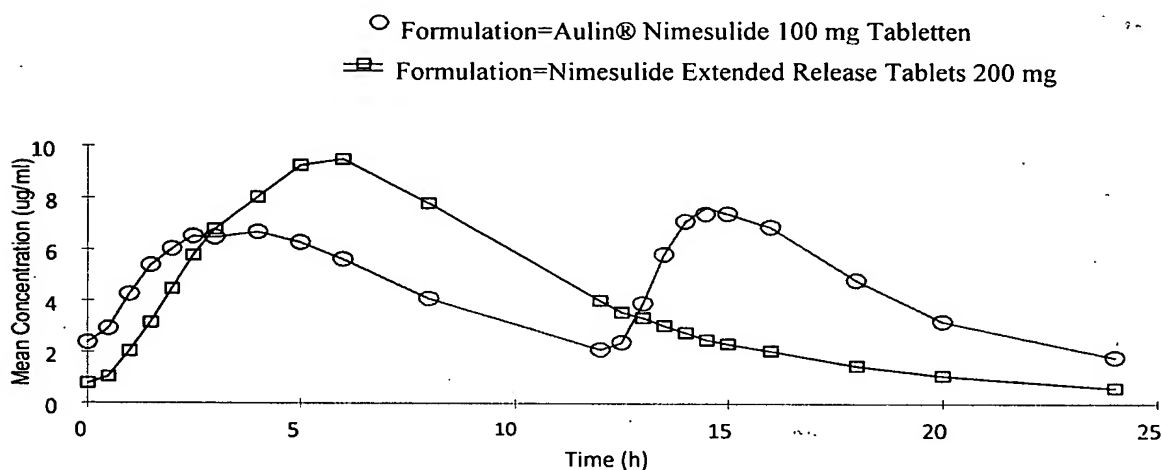


Fig. 2: Linear Plot of Mean Plasma Nimesulide Concentrations versus Time Profiles in Healthy Human Adult Male Subjects

Conclusion: The estimated relative extent of absorption for a steady-state dose of nimesulide ER based on $(AUC_{0-\tau_{ss}})$ is ~90% that for Aulin. Both the test and reference formulations were found to be well tolerated this study.

Conclusions from Pharmacokinetic Studies

Nimesulide Extended Release Tablets 200 mg have acceptable tolerability results as it does not exceed the exposure and peak plasma concentration compared to the conventional release 100 mg tablets taken twice daily for chronic pain management.

ANNEXTURE-2

Purpose: To compare the efficacy and safety of Nimesulide ER 200 mg (Willgo®) with Diclofenac SR 100 mg (Voveran®SR) in patients with osteoarthritis knee.

Study design: Open label, randomized, active-comparative controlled, multicentre, non-inferiority trial.

Methods: 262 patients aged > 45 years diagnosed to have osteoarthritis (OA) of the knee were randomized (1:1) in this multicentre study across India. Patients were allocated to receive either Willgo® (n = 131) or Voveran SR® (n = 131) tablet as per computer generated randomization once daily for a study treatment period of 30 days. Protocol assessment visits were on days 15 and 30. Primary efficacy endpoint was evaluated using VAS (Visual Analogue Scale) of 10 cm for pain at baseline, day 1 (multiple time points), day 15 and day 30. WOMAC OA index 3.1 was evaluated at enrollment and end of therapy. Nimesulide ER was to be considered non-inferior if the lower bound of 95% confidence interval (CI) for the treatment difference (Test - Reference) in mean VAS reduction for pain was less than 1 cm (clinically acceptable significant difference). Safety was evaluated by analyzing all reported clinical adverse events.

The study was conducted by using the standard tool available wherein primary efficacy endpoint was evaluated using VAS (Visual Analogue Scale) of 10 cm for pain and WOMAC OA index 3.1 (Western Ontario and McMaster Universities, osteoarthritis index) for pain + physical function was evaluated at enrollment and end of therapy.

Efficacy Criteria:

1) Primary endpoint

- a) Measurement of pain using a 10 cm VAS (Visual Analogue Scale)

2) Secondary endpoints

- a) Measurement of pain and function using WOMAC OA index
- b) Investigator global assessment of efficacy and tolerability using a 4-point scale
- c) Patient global assessment of efficacy and tolerability using a 4-point scale

Safety Criteria:

- All volunteered and observed adverse events (AEs)

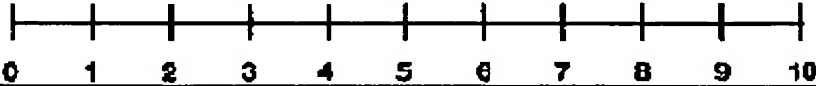
(ANNEXTURE- 2 Contd.....)

The WOMAC™ (Western Ontario and McMaster Universities) OA Index is used to assess subjects with OA knee or hip using 24 parameters. It can be used to monitor the course of the disease or to determine the effectiveness of medications. Parameters assessed as per the latest version of the instrument (WOMAC™ 3.1 Index) and scoring and interpreting the response to parameters on 10 cm VAS are given below:

Table 3: Parameters for WOMAC™ 3.1 Index

Pain (Pain + Stiffness)	Physical Function
<i>Pain:</i> (1) Walking on flat surface (2) Going up or down stairs (3) At night while in bed (4) Sitting or lying (5) Standing upright	(1) Descending stairs (13) Getting in/out of bath (2) Ascending stairs (14) Sitting (3) Rising from sitting (15) Going on/off toilet (4) Standing (16) Heavy domestic duties (5) Bending to floor (17) Light domestic duties (6) Walking on flat (7) Getting in/out of car (8) Going shopping
<i>Stiffness:</i> (1) After first wakening in the morning (2) After sitting, lying or resting later in the day	(9) Putting on socks/stockings (10) Rising from bed (11) Taking off socks/stockings (12) Lying in bed

• **Table 4 : Scoring and Interpretation of Response to parameters on 10 cm VAS**

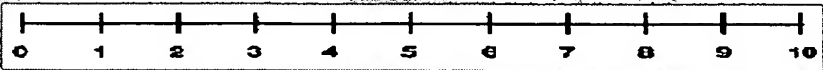
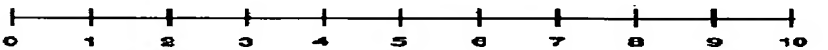
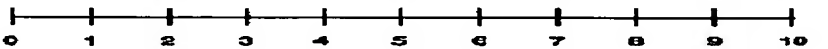
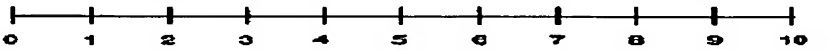
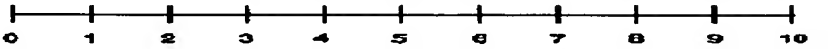
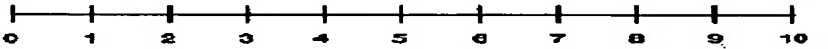
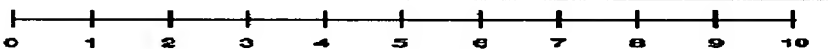
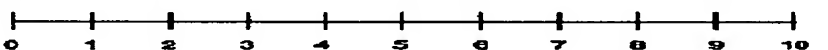
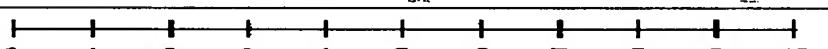
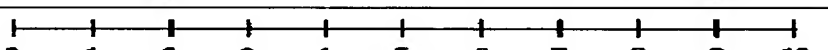
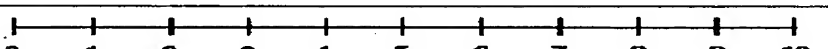
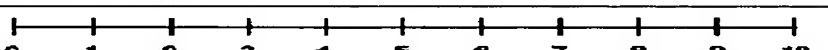
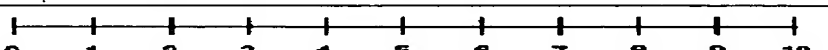
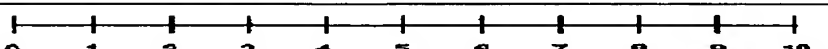
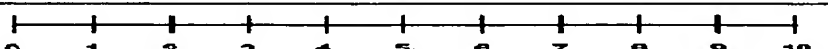
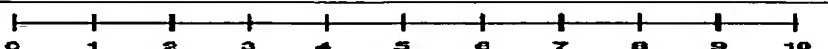
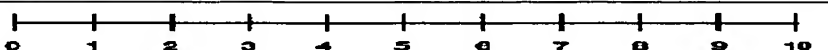
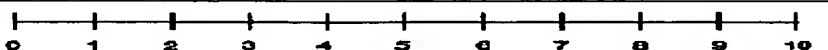

Total score = SUM
Average score = (Total score) / (number of items)
Interpretation Minimum average score: 0 (No pain) Maximum average score: 10 (Worst pain)

For further clarity please refer to patient diary card (sample in Table 5 below) used in the clinical studies to capture data for patients self rated assessment of pain and function using WOMAC OA index

(ANNEXTURE- 2 Contd.....)

(pain + physical function number of variables (7+17=24), scored 0-10 cm on VAS where 0 = No pain and 10 = Worst pain) using WOMAC™ OA Index (Version 3.1).

Table 5: PATIENT DIARY CARD

Patients Self Rated Assessment on WOMAC using Visual Analogue Scale		
<i>Self rated assessment to be completed by the patient based on their experience while performing respective activity</i>		
0-10 cm VAS		
Pain		
(1) Walking on flat surface		<input type="text"/>
(2) Going up or down stairs		<input type="text"/>
(3) At night while in bed		<input type="text"/>
(4) Sitting or lying		<input type="text"/>
(5) Standing upright		<input type="text"/>
Stiffness		
(1) After first wakening in the		<input type="text"/>
(2) After sitting, lying or resting later in the day		<input type="text"/>
Physical Function		
(1) Descending stairs		<input type="text"/>
(2) Ascending stairs		<input type="text"/>
(3) Rising from sitting		<input type="text"/>
(4) Standing		<input type="text"/>
(5) Bending to floor		<input type="text"/>
(6) Walking on flat		<input type="text"/>
(7) Getting in or out of car		<input type="text"/>
(8) Going shopping		<input type="text"/>
(9) Putting on socks / stockings		<input type="text"/>
(10) Rising from bed		<input type="text"/>

(ANNEXTURE-2 Contd..)

(11) Taking off socks / stockings		
(12) Lying in bed		
(13) Getting in/out of bath		
(14) Sitting		
(15) Going on/off toilet		
(16) Heavy domestic duties		
(17) Light domestic duties		
→ Patient's self rated global assessment of disease using 10 cm VAS including non-signal joints		

Results:

Efficacy

Non-Inferiority Primary Efficacy Analysis

Lower 95% CI of difference between treatment groups in mean change from baseline should be within 1 using a patient self-rated 10 cm VAS scale for pain.

The treatment difference, that is, Test - Reference (Willgo[®] - Voveran[®] SR) in mean VAS reduction, along with the associated 95% CI (defined by the lower limit (LL) and the upper limit (UL)), is shown in Table 6, using mITT study population.

Table 6: Difference in mean VAS reduction, with 95% CI

Product	Difference in mean VAS reduction (Nimesulide ER – Diclofenac SR)					
	95 % CI					UL
	Nimesulide ER	Diclofenac SR	NIM - DIC	LL		
	N	N				
Mean VAS reduction	119	5.46	119	4.87	0.59	-0.091 1.284

(ANNEXTURE- 2 Contd.....)

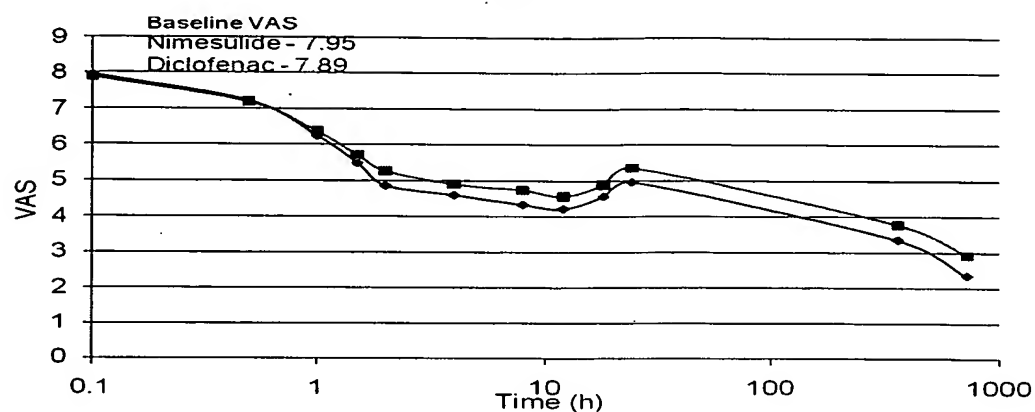
The interpretation of above table 6 is that - In mITT analysis mean VAS reduction was 5.46 for Nimesulide ER (Willgo[®]) and 4.87 for Diclofenac SR (Voveran[®] SR). The treatment difference (Nimesulide ER - Diclofenac SR) in mean VAS reduction was 0.59, with a lower bound 95% CI of -0.091, which was within the pre-specified non-inferiority margin of 1 cm.

Additional Efficacy Analysis: In both treatment arms statistically significant decrease in pain was observed from baseline to 30 min after treatment, with additional decrease occurring at subsequent hours on Day 1 and during observations made on Day 15 and Day 30. On Day 1, maximum pain relief was achieved after 12 h in both arms (45% and 41% reduction from baseline for Willgo and Voveran SR, respectively). The VAS scores obtained in the Willgo treatment group were lower than that in the Voveran SR treatment group at every assessment. Statistically significant lower scores were observed at 8 h (Day 1) and Day 30 for Willgo group as compared to the Voveran SR group ($p < 0.05$).

Table 7: VAS Score

Time Points	VAS Score	
	Nimesulide ER	Diclofenac SR
Baseline	7.95 ± 1.36	7.89 ± 1.46
0.5 hr	7.22 ± 1.69	7.19 ± 1.68
1 hr	6.25 ± 1.77	6.36 ± 1.84
1.5 hr	5.50 ± 1.92	5.71 ± 1.90
2 hr	4.87 ± 1.81	5.27 ± 1.88
4 hr	4.61 ± 1.56	4.90 ± 1.65
8 hr	4.34 ± 1.37*	4.74 ± 1.55
12 hr	4.23 ± 1.56	4.57 ± 1.55
18 hr	4.57 ± 1.43	4.89 ± 1.38
24 hr	4.97 ± 1.64	5.36 ± 1.51
Day 15	3.36 ± 1.77	3.78 ± 1.68
Day 30	2.35 ± 1.91*	2.93 ± 2.02
* $p < 0.05$		

Figure 3: VAS Score

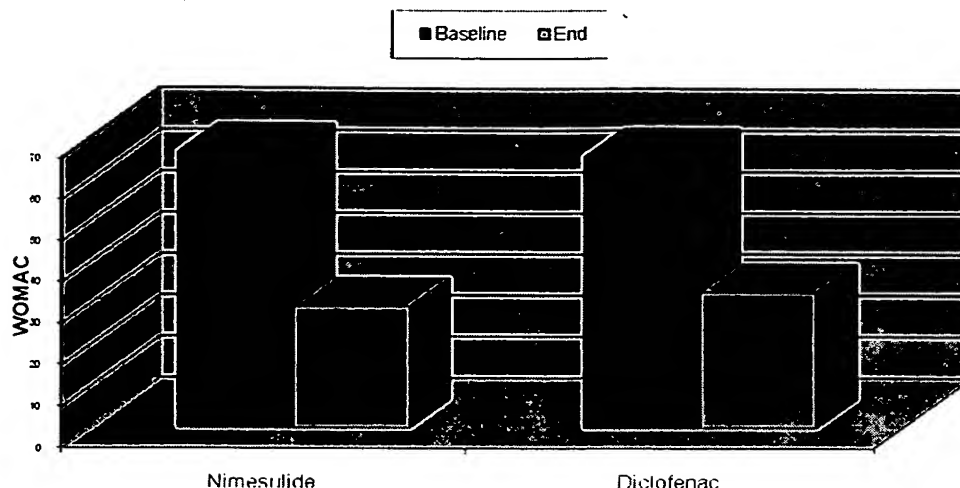


Conclusion: Nimesulide Extended Release Tablets 200 mg OD is non-inferior to Voveran SR (Diclofenac sodium) 100 mg OD in mean VAS Reduction for pain at 1 month in osteoarthritis knee. The novel ER product is expected to be more patient compliant alternative to the existing IR product.

Table 8: WOMAC index

Time points	WOMAC score	
	Nimesulide ER N=112	Diclofenac SR N=110
Baseline	66.57	65.58
End of therapy (Day 30)	29.22	32.58

Figure 4: WOMAC Index

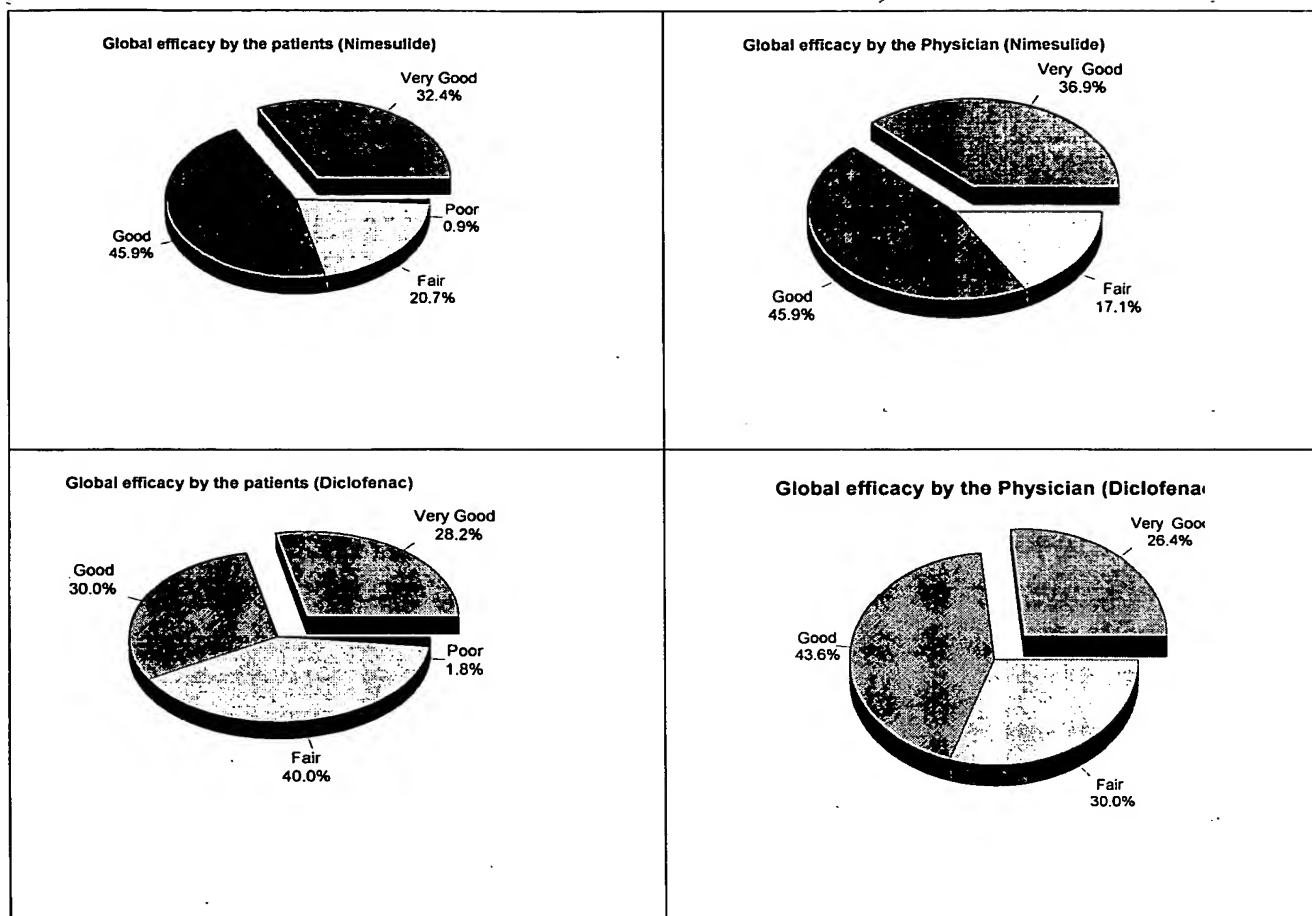


Conclusion: No statistically significant difference was observed in the WOMAC scores obtained in the two groups at baseline, as seen in Table 8 and Figure 4 (66.57 for Willgo and 65.58 for Voveran SR). Both groups exhibited a statistically significant decrease in WOMAC scores at the end of the therapy. The Willgo group had a favorable reduction over baseline (56.1%) as did Voveran SR (50.3%).

Global assessment of efficacy and Global tolerability by the Patient and Physician was evaluated on a 4-point scale

Global Efficacy: At day 30, both investigator and patient expressed their global assessment of efficacy of the treatment (Improvement as very good >75%, good >50% to 75%, Fair 25% to 50%, poor < 25%). According to investigator, positive (very good or good) outcomes were observed in 82.88% of the patients treated with Willgo compared with 70% of those treated with Voveran SR. Similar outcome were expressed by patients: 78.38% of the Willgo treated patients and 58.18% of the Voveran SR treated patients recorded a positive outcome as seen in Table 9 below.

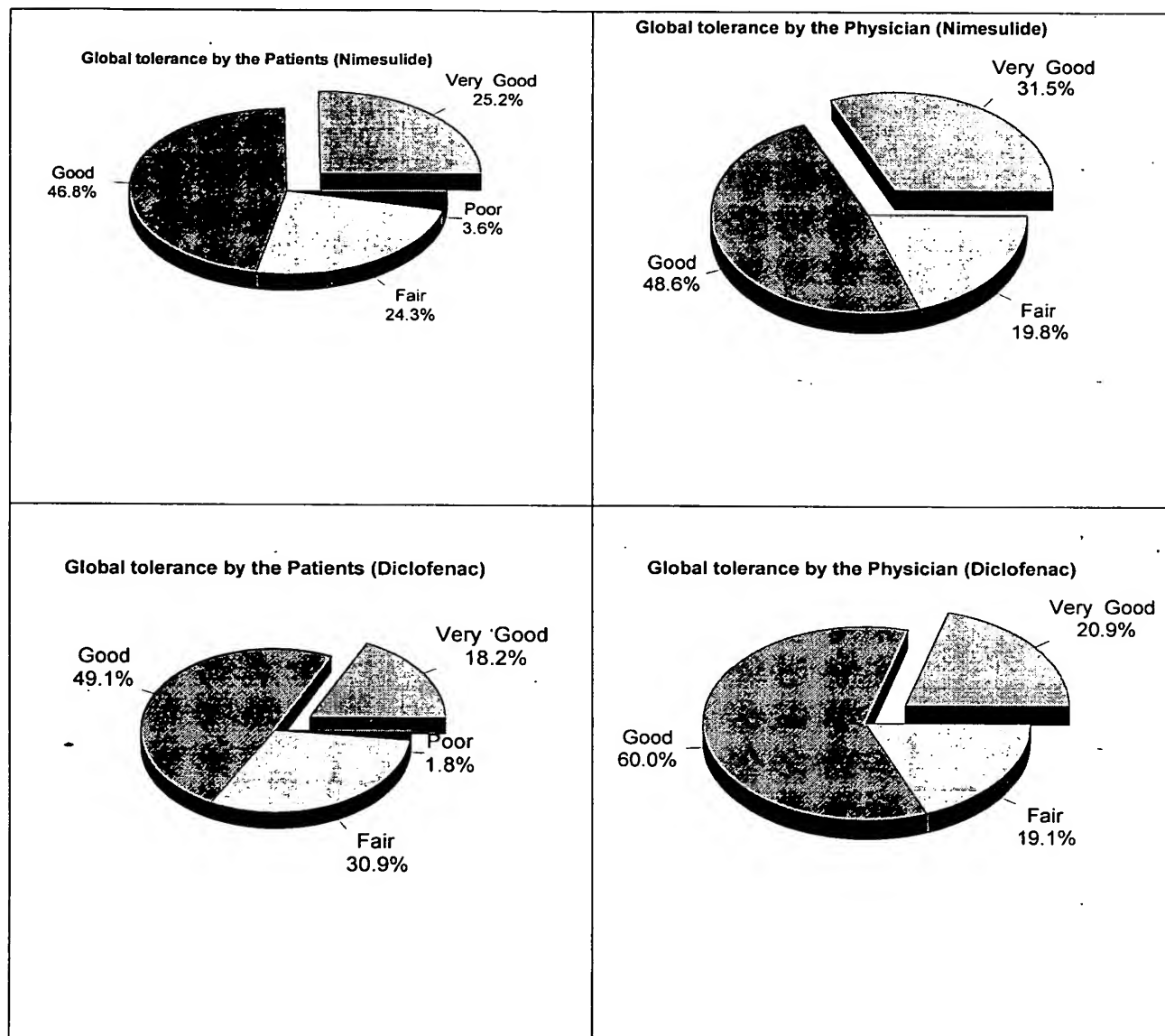
Table 9:



(ANNEXTURE- 2 Contd.....)

Global Tolerability: In tolerability assessment, investigator reported positive outcome (very good or good) in 80.18% patients in the Willgo group compared to 80.91% patients in the Voveran SR group. Positive outcome was reported by 72.08% patients in the Willgo group compared to 67.27% patients in the Voveran SR group as seen in Table 10 below.

Table 10:



(ANNEXTURE- 2 Contd.....)

Conclusion: Both the study treatment produced significant improvement in global assessment of efficacy and tolerability as assessed by the investigators and the patients.

Pharmacovigilance study on Nimesulide ER 200 mg (Willgo®)

The pharmacovigilance programme for Willgo® (Nimesulide Extended Release Tablets 200 mg) was conducted using the methodology similar to prescription-event monitoring (PEM).

Objectives: The objectives of this pharmacovigilance program were:

1. To capture adverse drug reactions (ADRs) suspected to be caused by Willgo®.
2. To gather data regarding prescription of Willgo®, by prescribers to form denominator for safety data collected.
3. To archive the safety information to develop a comprehensive safety database for Willgo®.
4. To compare the incidence rate of Willgo® with Nimesulide.

Methodology: This program had a methodology similar to prescription event monitoring. Data for this program were gathered from 1826 prescribers (physicians, orthopedists, surgeons, dentists, etc.) who participated in the Willgo® Pharmacovigilance program from 161 cities all over India. The participation of prescribers was voluntary with no incentives attached.

Each of the participating prescribers were supplied with a pharmacovigilance booklet containing a prescription log sheet, suspected ADR reporting forms, a project flow-chart, a Willgo® package insert and information about pharmacovigilance program. Self-addressed Business Reply Envelopes were provided to the prescribers, and a monthly reminder email was sent to all prescribers participating in this pharmacovigilance program.

The prescribers sent back the data in the form of prescription log sheets and suspected ADR forms. A provision was kept for adding any ADR report spontaneously generated (by a prescriber not participating in this pharmacovigilance program) and sent directly to the sponsor. The prescription log sheets and ADR forms as received were entered in the database.

Prescription event monitoring program to capture adverse drug reactions suspected to be caused by Nimesulide ER (Willgo®) involving a total of 112,730 patients who were prescribed Willgo.

(ANNEXTURE- 2 Contd.....)

The total exposure was 1,321,449 patient days and the mean exposure was 11.72 ± 8.47 days.

While analyzing the data, it was assumed that all the patients being prescribed Willgo® would be exposed to it for the said period; and those patients who did not report to the prescriber did not have any adverse reaction. For calculating the number of patients, patients with multiple prescriptions refill, etc. were counted as one, and duplicated entries were excluded. Any adverse reaction report related to the use of Willgo®, also, is included in the numerator, whether or not the reporter was a prescriber participating in this Pharmacovigilance program. The denominator for the drug usage was obtained by using number of prescriptions (~exposure days).

Results:

A comparison for the rate of occurrence of suspected ADRs expressed in standard category of frequency, i.e. very common ($>1/10$); common (frequent) ($>1/100$, $<1/10$); uncommon ($>1/1,000$, $<1/100$); rare ($>1/10,000$, $<1/1,000$) and very rare ($<1/10,000$) according to summary of product characteristics (SPC) is shown in Table 11. In the EMEA SPC of “Nimesulide” 100 mg tablet²³, the listing of undesirable effects is based on data from controlled clinical trials (approximately 7,800 patients) and from post marketing surveillance.

Table 11: Comparison of the frequency of suspected ADRs

Body system/ADR term	Present Study	EMEA SPC of “Nimesulide”
Blood disorders		
Anaemia	Not reported	Rare
Eosinophilia	Not reported	Rare
Thrombocytopenia	Not reported	Very rare
Pancytopenia	Not reported	Very rare
Purpura	Not reported	Very rare
Immune system disorders		
Hypersensitivity	Not reported	Rare
Anaphylaxis	Not reported	Very rare
Metabolism and nutrition disorders		
Hyperkalaemia	Not reported	Rare
Psychiatric disorders		
Anxiety	Not reported	Rare
Nervousness	Not reported	Rare
Nightmare	Not reported	Rare
Nervous system disorders		

Dizziness	Very rare	Uncommon
Headache	Not reported	Very rare
Somnolence	Very rare	Very rare
Encephalopathy (Reye's syndrome)	Not reported	Very rare
Eye disorders		
Vision blurred	Not reported	Rare
Visual disturbance	Not reported	Very rare
Ear and labyrinth disorders		
Vertigo	Very rare	Very rare
Cardiac disorders	Not reported	Rare
Tachycardia		
Vascular disorders		
Hypertension	Not reported	Uncommon
Haemorrhage	Very Rare	Rare
Blood pressure fluctuation	Not reported	Rare
Hot flushes	Not reported	Rare
Respiratory disorders		
Dyspnoea	Not reported	Uncommon
Asthma	Not reported	Very rare
Bronchospasm	Not reported	Very rare
Gastrointestinal disorders		
Diarrhoea	Very rare	Common
Nausea	Very rare	Common
Vomiting	Very rare	Common
Constipation	Not reported	Uncommon
Flatulence	Very rare	Uncommon
Gastritis	Very rare	Uncommon
Abdominal pain	Very rare	Very rare
Dyspepsia	Very rare	Very rare
Stomatitis	Very rare	Very rare
Melaena	Not reported	Very rare
Gastrointestinal bleeding	Very rare	Very rare
Duodenal ulcer and perforation	Not reported	Very rare
Gastric ulcer and perforation	Not reported	Very rare
Hepato-biliary disorders		
Hepatitis	Not reported	Very rare
Fulminant hepatitis (including fatal cases)	Not reported	Very rare
Jaundice	Not reported	Very rare
Cholestasis	Not reported	Very rare
Skin and subcutaneous tissue disorders		
Pruritis		
Rash	Very rare	Uncommon
Increased sweating	Very rare	Uncommon
Erythema	Not reported	Uncommon
Dermatitis	Not reported	Rare
Urticaria	Not reported	Rare

Angioneurotic oedema	Very rare	Very rare
Face oedema	Not reported	Very rare
Erythema multiforme	Very rare	Very rare
Stevens Johnson syndrome	Not reported	Very rare
Toxic epidermal necrolysis	Not reported	Very rare
Renal and urinary disorders		
Dysuria	Not reported	Rare
Haematuria	Not reported	Rare
Urinary retention	Not reported	Rare
Renal failure	Not reported	Very rare
Oliguria	Not reported	Very rare
Interstitial nephritis	Not reported	Very rare
General disorder		
Oedema	Rare	Uncommon
Malaise	Not reported	Rare
Asthenia	Not reported	Rare
Hypothermia	Not reported	Very rare
Investigations		
Hepatic Enzymes increased	Not reported	Common

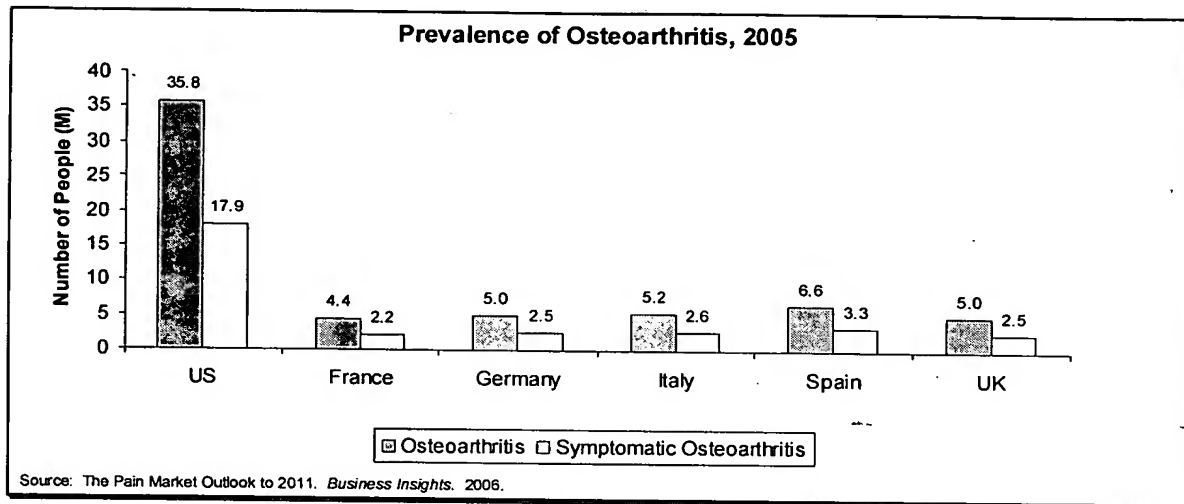
Conclusion: The results of the current study, coupled with the results of previous studies, demonstrate that Nimesulide Extended Release Tablet 200 mg is well tolerated and safe for treatment of osteoarthritis, rheumatoid arthritis and other painful inflammatory conditions.

No major adverse cardiovascular event has been reported in any of the above clinical trials and prescription event monitoring program.

ANNEXTURE-3

Osteoarthritis (OA) is a progressive bone and joint disorder that can lead to severe joint pain and decreased patient mobility. It is estimated that within the US and the EU the prevalence of osteoarthritis is approximately 62 million people. About half of these patients (31 million) experiences pain related to OA (Symptomatic OA). The prevalence of people with symptomatic OA is estimated at 17.9 million (6.1% of the total population) in the US and 13.1 million (4.3%) for the top five largest European markets.⁶

Fig 5:



The prevalence of OA rises with age. In fact – in the US, the over-65 population accounts for more than half of all OA cases. The prevalence of OA rises from 8.4% in patients aged 35-44 to 41.4% for patients above the age of 65.⁷ The anticipated growth in the elderly population is anticipated to result in an increased prevalence of OA in the major global markets. The US is expected to have an additional 9 million more people aged 65 and older in 2020 than in 2006.

Osteoarthritis Treatment Paradigm

First-line treatment options for OA (acetaminophen and lifestyle recommendations) are successful to a limited extent. Patients typically shift to either traditional NSAIDs or selective COX-2 inhibitors as second-line therapy. Some patients may progress further and require treatment for flare-ups (corticosteroids, hyaluronic acid) or invasive surgery.

(ANNEXTURE-3 Contd...)

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely available for decades. Due to their well-established efficacy and dosing profile, they remain commonly used agents for mild-to-moderate OA. However, they may cause serious GI side effects with long-term use. Long-term use of any of the traditional NSAIDs, may damage the mucous layer of the stomach, resulting in general stomach discomfort or, more seriously bleeding and ulcer formation.

Selective COX-2 inhibitors are a subset of NSAIDs that specifically inhibit the COX-2 enzyme. The intent of this specificity is to reduce GI side effects commonly associated with the traditional NSAIDs. However, the COX-2 class has been associated with a higher incidence of cardiovascular side effects.

Treatment Choices

Physicians make their treatment choice based on four primary factors since comparative studies have found no clear efficacy differences:

- Dosing and Frequency
- Gastrointestinal Risks
- Cardiovascular Risks
- Renal Risks

Physicians must balance the different risks based on individual patient circumstances – but none of the current therapies provide the combination of simplified dosing with minimal GI, cardiovascular and renal risks.⁸

Nimesulide Extended Release tablet is positioned to meet the identified unmet needs with current therapeutics for the treatment of OA. Panacea Biotec's brand Willgo[®], based on the present invention (bilayered, controlled release Nimesulide tablets), sold in India, has been proven to be a highly effective product for the management of chronic OA pain and inflammation offering the advantage of once a day dosing with favorable GI tolerability and good safety in Cardio Vascular and Renal parameters. A major challenge that was overcome by the present invention was the development of an extended release

(ANNEXTURE-3 Contd...)

formulation despite the region specific absorption of Nimesulide from the upper parts of GIT.

The product was introduced in India as a new drug delivery product supported by promising clinical trial results. The product (marketed under the brand name Willgo®) was able to address a significant unmet medical need which resulted in consistently growing sales. As an example the IMS-ORG audited data for the last three years is presented below:

Table 12: Sales of Willgo® Tablet (Extended Release Nimesulide) and Nimulid® Tablet (Immediate Release Nimesulide) in India

OUR BRANDS	Apr-Dec 06	MAT DEC 07	MAT DEC 08	Apr-Dec 06	MAT DEC 07	MAT DEC 08
	ABS Value	ABS Value	ABS Value	ABS Units	ABS Units	ABS Units
WILLGO TABS	23,555,210	34,804,568	42,599,763	594,829	863,637	995,150
NIMULID TABS	94,715,001	106,154,891	102,530,488	4,079,327	4,313,504	4,168,075

ABS Value means Absolute Amount in Rupees

ABS Units means Absolute Number of Strips of Each Brand (Each Strip contains 10 Tablets)

MAT Means Moving Annual Total

TABS means Tablets

The Table 1 indicates the sales growth of Willgo® Tablet (Extended Release Tablet) and Nimulid® Tablet (Immediate Release Tablet) in absolute value and units for the period i.e. Apr 2006 to Dec 2006, Jan 2007 to Dec 2007 and Jan 2008 to Dec 2008.

Conclusion: It has been concluded from the above table that the sales growth of Willgo® (Extended Release Nimesulide) is increasing year by year. Percentage growth Sales of Willgo® has increased by 80.8% in last two years from Dec 2006 to Dec 2008. While percentage sales growth of Nimulid® Tablet (Immediate Release Nimesulide) has increased only by 8.25 in last two years from Dec 2006 to Dec 2008 and decreased by 3.4 in last one year from Dec 2007 to Dec 2008.

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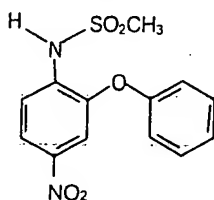
On the safety of nimesulide, a preferential COX-2 inhibitor

S. K. Kulkarni

Nimesulide, a preferential COX-2 inhibitor is a non-carboxylic acid nonsteroidal anti-inflammatory drug (NSAID) that has been effectively used for the treatment of a variety of inflammatory and painful conditions, including osteoarthritis in European and Asian countries for more than 15 years. Its market share is reported to be fifth amongst the NSAIDs in the worldwide market¹. It was introduced in the Indian market in the early 1990s. Unlike other classical NSAIDs, it has high gastrotolerability due to its relatively high pK_a value (6.5) and preferential COX-2 selectivity (COX-2/COX-1 = 0.19). This is perhaps one of the reasons (high efficacy and low gastric intolerance) that the drug is marketed in more than 50 countries, including India. There are more than 70 brands available in the Indian market. The drug is also available in a fixed dose combination with serratiopeptidase, a proteolytic enzyme and other classes of agents, but its combination with paracetamol needs critical evaluation as regards its rationality.

Chemical structure of nimesulide:

Chemical name: N-(4-nitro-2-phenoxyphenyl) methanesulfonamide; empirical formula: C₁₃H₁₂N₂O₅S; molecular weight: 308.31; CAS-number: 51803-78-2.



Pharmacological basis of use of nimesulide

Nimesulide is chemically different from other drugs in this class because of the sulfonanilide moiety. Like all NSAIDs, nimesulide acts by inhibiting the synthesis of prostaglandins as a consequence of blockade of the enzyme cyclooxygenase (COX). Two isoforms of the COX isoenzyme are known, COX-1 and COX-2. COX-1 is constitutively expressed in most cells and elaborates prostanoids involved in various physiological processes, i.e.

maintaining gastromucosal integrity and renal function (housekeeping functions). COX-2 is induced by proinflammatory cytokines and mitogens at sites of inflammation/tissue injury. Nimesulide has potent analgesic, anti-inflammatory and antipyretic activities on oral and rectal administration². By respecting the activity of COX-1, nimesulide possesses a much lower risk for gastroduodenal lesions in comparison to classical NSAIDs. Nimesulide is reported to be a preferential COX-2 inhibitor in human blood assays (5–20-fold greater potency against COX-2 than COX-1). Besides COX-2 activity, nimesulide inhibits the production of oxygen free radicals, long-lived monochloramines, hypochlorous acid formed from activated neutrophils and other inflammatory cells. It is also reported to inhibit the release of histamine from the mast cells and basophils, and the production of PAF by neutrophils. Nimesulide has phosphodiesterase IV inhibiting property as well, and has antiprotease effect against neutrophil elastase, cartilage collagenase and stromelysin. The potent anti-inflammatory and analgesic activities of the drug are seen in a number of experimental models of inflammation, i.e. carrageenan-induced paw-oedema, adjuvant-induced arthritis, Randall Sellito test, UV-induced skin erythema and phenylquinone-induced writhing tests in mice³. In acute and chronic inflammatory conditions in patients, nimesulide is found to be more effective than placebo and had comparable anti-inflammatory activity with established NSAIDs. Epidemiological data suggested that long-term therapeutic use of nimesulide at anti-inflammatory doses (100 mg, twice daily) did not cause serious gastrointestinal symptoms. Nimesulide is also safe in aspirin-sensitive asthmatic patients. It is reported to be beneficial in relieving the symptoms of rhinitis, rhinopharyngitis, tubaritis and secretory otitis media with concomitant antibiotic treatment.

Therapeutic indications

Because of its peculiar multi-factorial mode of action, nimesulide perhaps has

demonstrably superior activities in painful and inflammatory conditions. It is mainly indicated for joint inflammation, osteoarthritic pain, fever, musculoskeletal conditions, acute pain including that from perioperative conditions, and dysmenorrhea. The daily-recommended dosage is 100 mg b.i.d. for these clinical situations.

Safety

Pharmacoepidemiological studies suggest that nimesulide is an effective NSAID with relatively favourable profile of safety for the treatment of osteoarthritis and non-rheumatoid musculo-skeletal conditions⁴. Clinically observed adverse events with nimesulide have been typical of those found with other NSAIDs⁵. Further, a post-marketing surveillance of nimesulide suspension (50 mg/ml), conducted through 600 pediatricians all over India, also indicates the absence of nimesulide-related hepatotoxicity in children⁶. The incidence of rare and unpredictable liver reactions with nimesulide is about 0.1 per 100,000 treated patients, which is not higher than most of the other NSAIDs⁷ like diclofenac^{8,9}.

Further, the individual or inherent risk factors of the patient can predispose him/her to increased risk for development of nimesulide-associated unpredictable or idiosyncratic hepatic reactions. These include specific gene abnormalities, alteration in specific gene expression or epigenetic factors. The wide clinical efficacy with unique pharmacodynamic actions and beneficial gastrotolerability and bronchotolerability in comparison with other NSAIDs may outweigh the relative risk of nimesulide-associated liver reaction (common to the class NSAIDs) in the long-term use of the drug.

Present debate in India on nimesulide use

As stated earlier, nimesulide was introduced in the Indian market in the early 1990s for the management of pain, fever and inflammatory conditions. Recently, nimesulide has been under controversy due to alleged hepatotoxicity. Moreover,

the favourable efficacy and safety of nimesulide in different clinical situations in pediatric as well as adult population have been demonstrated by its virtual presence on the prescription in more than 50 countries, both developed and developing, in the last 17 years. Recently, controversial and ambiguous reports highlighted by the media on the grounds of isolated reported cases of hepatotoxicity without any known, conclusive and predictable drug-induced evidences have raised concern on the prescription use of nimesulide. The report of unexpected liver reaction to nimesulide may be viewed as a class phenomenon that occurs with all NSAIDs, including diclofenac, sulindac, etc.¹⁰. Many a times such adverse propaganda is market-force initiated. The present case is no different, if one analyses the global extent of its relative use and market share of the product.

In India, the sales of nimesulide oral solids have reached 1200 lac units of 10's with a consistent growth of 18% in the last three years, with Nise® and Nimulid®, being the two top-most leading brands. In an international survey (Brand Poll report) carried out on 300 doctors in Europe to assess the most recognized brands of anti-inflammatory drugs (product awareness), Nimesulide (Aulin®) not only ranked third in brand awareness, but it was also perceived as the most effective and one of the most safest drugs (perceived quality) in the NSAID market.

The safety profile of the drug is currently under review by the Committee for Proprietary Medicinal Products after temporary suspension in Finland, Spain and Turkey due to suspected serious drug adverse reaction. Helsinki, the first pharmaceutical company which had marketed the drug, is confident that nimesulide has a positive risk benefit profile, and will support such a concept with a group of top international experts in the ongoing discussion with European Agency for the Evaluation of Medicinal Products. Following the Irish Medical Board's 1999 review, the company was requested to perform post-marketing authorization studies to address the safety issues. A pilot study in 500 Irish patients suggested that the safety profile of nimesulide was similar to that of other NSAIDs. An observational study in 9000 Irish patients, comparing the safety profile of nimesulide with diclofenac and ibuprofen, the other two older NSAIDs, is currently under way. Interim data provided by the company on 1212 patients

indicated that at this stage, there was no apparent difference in the safety profile of the three treatments.

Considering all the views of the alleged hepatotoxicity, the Drug Controller General of India (DCGI) has constituted a subcommittee of Drug Technical Advisory Board, a statutory body under the Drugs and Cosmetics Act 1940, Govt of India to review the clinical status of nimesulide. The sub-committee which met on 9 October 2002 has opined to obtain the views/experiences from a few leading manufacturing companies of nimesulide formulation in India, as to whether they have received any severe adverse drug reaction reports from their field force or from medical practitioners. Meanwhile, post-marketing surveillance data are also being collected. Two years ago, a debate on the irrational combination of paracetamol with nimesulide had also led to the ban of this combination by the DCGI¹¹.

Drug control issues which lead to marketing of irrational combinations

The Indian laws have not been properly defined to grant marketing approvals of the fixed dose combinations (FDCs) by state or central drug controlling authorities. Therefore, the state drug controlling authorities have continuously been approving various FDCs lacking any pharmacodynamic or pharmacokinetic advantages and acceptable rationale, for example, nimesulide-paracetamol combination, without prior permission from the DCGI. Such type of approval without any pre-clinical and clinical studies leads to marketing of prescription-based irrational combinations.

FDC products are those which have two or more drugs present in a fixed ratio, where one of the drugs either potentiates or synergizes the effect of the other, or the symptomatic relief provided by the two of them differs in nature in the same disorder.

As per Rule 122B, D, E(C) (Appendix VI of Schedule Y) of the Drugs and Cosmetics Act of India, FDCs fall into four categories:

- (a) The first group includes those in which one or more of the active ingredients is a new drug.
- (b) The second group includes those in which active ingredients already appro-

ved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

(c) The third group includes those which are already marketed, but in which it is proposed either to change the ratio of the active ingredients or to make a new therapeutic claim.

(d) The fourth group includes those whose active ingredients have been widely used in particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form, and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

The groups (a)–(c) require adequate clinical data and the group (d) requires acceptable rationale that has to be submitted along with the application to get the marketing approval of FDC by DCGI, and not by individual state authorities. It may be of interest to mention that the model list of essential drugs prepared by WHO has only eight essential FDCs (WHO Technical Report 825, 1992), which would meet the medical needs of majority of the population.

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CAN J PHYSIOL PHARMACOL

Citations:

75(*):1088-95 1997

Author:

Riendeau D, Charleson S, Cromlish W, Mancini JA, Wong E, Guay J.

Title:

Comparison Of The Cyclooxygenase-1 Inhibitory Properties Of Nonsteroidal

ISSN:

12057541

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Comparison of the cyclooxygenase-1 inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, using sensitive microsomal and platelet assays

Denis Riendeau, Stella Charleson, Wanda Cromlish, Joseph A. Mancini, Elizabeth Wong, and Jocelyne Guay

Abstract: Two forms of cyclooxygenase (COX) activity are involved in the synthesis of prostaglandins, prostacyclins, and thromboxanes in mammalian cells. There is now convincing evidence, obtained with a number of structurally distinct inhibitors, that selective COX-2 inhibitors possess anti-inflammatory effects with an improved gastrointestinal tolerability compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) affecting both COX-1 and COX-2. As more selective COX-2 inhibitors are being developed, assays with a high degree of sensitivity to inhibition are needed to compare the relative effects of compounds on COX-1 activity. In the present report, we describe a sensitive assay for the inhibition of human COX-1 based on the production of prostaglandin E_2 by microsomes from U937 cells incubated with a subsaturating concentration of arachidonic acid. More than 45 NSAIDs and selective COX-2 inhibitors were tested in this assay. IC_{50} values ranged from 1 nM for flunixin and flurbiprofen to about 200–500 μ M for salicylate and acetaminophen. Potent and nonselective NSAIDs such as sulindac sulfide, diclofenac, and indomethacin showed IC_{50} values of <20 nM. Among the compounds that have been reported to show selectivity for COX-2, the rank order of potency against COX-1 was DuP 697 > SC-58451 > celecoxib > nimesulide ~ meloxicam ~ piroxicam ~ NS-398 ~ RS-57067 > SC-57666 > SC-58125 > flosulide > etodolac > L-745,337 > DFU ~ T-614, with IC_{50} values ranging from 7 nM to 17 μ M. A good correlation was obtained between the IC_{50} values for the inhibition of microsomal COX-1 and both the inhibition of TXB_2 production by Ca^{2+} ionophore challenged platelets and the inhibition of prostaglandin E_2 production by CHO cells stably expressing human COX-1. However, the microsomal assay was more sensitive to inhibition than cell-based assays and allowed the detection of inhibitory effects on COX-1 for all NSAIDs and selective COX-2 inhibitors examined with discrimination of their potency under conditions of limited availability of arachidonic acid.

Key words: cyclooxygenase, prostaglandin synthase, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, platelets, gastrointestinal toxicity

Résumé : Deux formes d'activité de la cyclo-oxygénase (COX) participent à la synthèse des prostaglandines, des prostacyclines et des thromboxanes dans les cellules des mammifères. Des faits probants, obtenus au moyen de divers inhibiteurs de structures distinctes, indiquent que les inhibiteurs sélectifs de la COX-2 possèdent des effets anti-inflammatoires offrant une plus grande tolérance gastro-intestinale que les anti-inflammatoires non stéroïdiens conventionnels (AINS) affectant tant COX-1 que COX-2. Avec la mise au point d'inhibiteurs plus sélectifs de la COX-2, on doit envisager l'emploi d'essais plus sensibles à l'inhibition pour comparer les effets relatifs des composés sur l'activité de la COX-1. Dans la présente étude, nous décrivons un essai sensible pour évaluer l'inhibition de la COX-1 humaine; cet essai est basé sur la production de prostaglandine E_2 par les microsomes de cellules U937 incubés avec une concentration sous-saturante d'acide arachidonique. Plus de 45 AINS et inhibiteurs sélectifs de la COX-2 ont été testés dans cet essai. Les valeurs de IC_{50} étaient comprises entre 1 nM pour le flunixin et le flurbiprofène et 200–500 μ M pour le salicylate et l'acétaminophène. Des AINS non sélectifs et plus puissants, comme le sulindac, le diclofénac et l'indométacine, ont montré des valeurs de IC_{50} < 20 nM. Parmi les composés ayant montré une sélectivité pour COX-2, l'ordre de puissance contre COX-1 a été le suivant : DuP 697 > SC-58451 > célécoxib > nimesulide ~ méloxicam ~ piroxicam ~ NS-398 ~ RS-57067 > SC-57666 > SC-58125 > flosulide > étodolac > L-745,337 > DFU ~ T-614, avec des valeurs de IC_{50} comprises entre 7 nM et 17 μ M. Une bonne corrélation a été obtenue entre les valeurs de IC_{50} pour l'inhibition de la COX-1 microsomale et l'inhibition de la production de thromboxane B_2 par les plaquettes stimulées à l'ionophore du Ca^{2+} , et celles pour l'inhibition de la production de prostaglandine E_2 par les cellules CHO exprimant de manière stable la COX-1 humaine. Toutefois, l'essai

Received April 18, 1997.

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microsomal est plus sensible à l'inhibition que les essais cellulaires, et il permet de détecter les effets inhibiteurs sur la COX-1 de tous les AINS et inhibiteurs sélectifs de la COX-2 examinés, et d'évaluer leur puissance dans des conditions de disponibilité limitée d'acide arachidonique.

Mots clés : cyclo-oxygénase, prostaglandine synthase, anti-inflammatoires non stéroïdiens, inhibiteurs de COX-2, plaquettes, toxicité gastro-intestinale.

[Traduit par la Rédaction]

Introduction

Cyclooxygenase (COX) catalyses the oxygenation of arachidonic acid to prostaglandin (PG) H_2 as the first step in the synthesis of prostaglandins, prostacyclins, and thromboxanes in mammalian cells. COX-1 is the major enzyme form found in healthy tissues and plays a role in thrombogenesis and in the homeostasis of the gastrointestinal tract and kidneys. COX-2 is inducible by endotoxin, cytokines, and mitogens and has been associated with the elevated production of prostaglandins observed during inflammation, pain, and pyretic responses (Bakke and Botting 1996; Herschman 1996; Vane and Botting 1995).

Most of the classical nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, ibuprofen, or diclofenac inhibit both COX-1 and COX-2 with little or no selectivity for a particular cyclooxygenase isoform (Battistini et al. 1994; O'Neill et al. 1994). It is now well recognized that the administration of NSAIDs to animals results in gastrointestinal lesions and that the occurrence of gastrointestinal ulceration and bleeding is a major side effect associated with the chronic use of NSAIDs (Allison et al. 1992; Langman et al. 1994; Traversa et al. 1995). These effects have been attributed to the inhibition of the synthesis of prostaglandins derived from COX-1, resulting in alterations of the regulation of mucosal blood flow, mucous and bicarbonate secretion, and tumor necrosis factor- α (TNF α) production. Other factors, such as topical irritation and enterohepatic recirculation of the drugs, have also been considered in the process of NSAID-induced gastropathy (Appleyard et al. 1996; Hudson et al. 1992; Rainsford 1992; Whittle 1992). Additional evidence for the implication of COX-1 inhibition in NSAID-induced gastric damage has been provided by recent studies with selective COX-2 inhibitors demonstrating that these compounds are effective anti-inflammatory agents with a marked decrease of ulcerogenicity in healthy animals compared with known NSAIDs (Chan et al. 1995; Futaki et al. 1994; Gans et al. 1990; Masferrer et al. 1994; Riendeau et al. 1997). Current clinical studies with the selective COX-2 inhibitors celecoxib (Hubbard et al. 1996) and MK-966 (Ehrlich et al. 1996) should allow the evaluation of the therapeutic advantages of selective COX-2 inhibition.

Previous studies with the selective COX-2 inhibitors NS-398, DuP 697, and DFU have shown that these compounds are time-dependent inhibitors of COX-2 and rapidly reversible competitive inhibitors of COX-1 (Copeland et al. 1994; Ouellet and Percival 1995; Riendeau et al. 1997). Assays with recombinant enzymes are typically performed using arachidonic acid concentrations ranging from 1 to 10 μ M to evaluate inhibitor selectivity (Gierse et al. 1995; Laneuville et al. 1995; Leblanc et al. 1995). Several of the selective COX-2 inhibitors show no inhibitory effects on COX-1 activity under these conditions, with the detection of inhibition at high doses being sometimes

limited by compound insolubility in aqueous media. We have previously reported that inhibition of COX-1 activity by selective COX-2 inhibitors can be detected using microsomes from U937 cells incubated with a low concentration of arachidonic acid (Riendeau et al. 1997). In this study, the inhibitory effects of a large number of NSAIDs and COX-2 inhibitors on COX-1 activity were evaluated under conditions of limited arachidonic acid availability and were compared with those observed with platelet and whole-cell assays.

Materials and methods

NSAIDs and COX-2 inhibitors

Acetaminophen, salicylic acid, isoxicam, niflumic acid, carprofen, phenylbutazone, meclofenamic acid, mefenamic acid, flufenamic acid, nabumetone, diclofenac, fenoprofen, ketoprofen, nimesulide, piroxicam, naproxen, zomepirac, etodolac, and ibuprofen were obtained from Sigma Chemicals (St. Louis, Mo.). Indomethacin, acetylsalicylic acid, and flurbiprofen were purchased from Cayman Chemicals, Ann Arbor, Mich. Flunixin (banamine) was obtained from Schering-Plough, Pointe-Claire, Que., and ketorolac from Roche Bioscience, Mississauga, Ont. Tenidap (Moore et al. 1996) was provided by the Central Research Division, Pfizer, Groton, Conn. Sulindac sulfide, azapropazone, fenclofenamic acid, benoxaprofen, tepoxalin, NS-398 (Futaki et al. 1994), DuP 697 (Gans et al. 1990), flosulide (CGP 28238) (Wiesenberg-Bottcher et al. 1989), meloxicam (Engelhardt et al. 1996), 6-methoxy-2-naphthaleneacetic acid (6-MNA) (Blower 1992), SC-58451 (Reitz et al. 1995), SC-58125 (Seibert et al. 1994), SC-57666 (Reitz et al. 1994), L-745,337 (Chan et al. 1995), 6-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-2H-pyridazin-3-one (RS-57067) (Barnett et al. 1996), T-614 (Tanaka et al. 1995), celecoxib (Hubbard et al. 1996), L-745,296 (compound 23, Leblanc et al. 1995), and 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl-2(5H)-furanone (DFU) (Riendeau et al. 1997) were synthesized in the Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, Canada, or were obtained from Merck Research Laboratories, Rahway, N.J.

Inhibition of microsomal COX-1 at low arachidonic acid concentration

U937 cells were obtained from the American Type Culture Collection and cultured in spinner flasks in RPMI (Sigma Chemical) supplemented with 2 g/mL $NaHCO_3$, 50 IU/mL penicillin, 50 μ g/mL streptomycin, and 10% heat inactivated fetal bovine serum. These cells express COX-1 and no detectable amounts of COX-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoblot analyses (Wong et al. 1997). Undifferentiated U937 cells were harvested by centrifugation at 500 \times g for 5 min, washed once with phosphate-buffered saline (Gibco-BRL, Burlington, Ont.), repelleted, and stored at $-80^\circ C$ until processing. Cells were thawed and resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2 mg/mL leupeptin, 2 mg/mL soybean trypsin inhibitor, 2 mg/mL aprotinin, and 1 mM phenylmethylsulfonyl fluoride (typically 1×10^{10} cells in 250 mL of buffer). The cell suspension was sonicated 4 times for 10 s (Cole Parmer Ultrasonic Homogenizer 4710, Cole Parmer Instrument Co.,

Chicago, Ill.; output control, 3.8; 70% duty cycle) and then centrifuged at $10\,000 \times g$ for 10 min at 4°C . The supernatant was centrifuged at $100\,000 \times g$ for 1 h at 4°C , and the resulting pellet was resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA. Aliquots of the resuspended pellet, referred to as the microsomal preparation (7–20 mg of protein/mL), were stored at -80°C . Protein concentrations were determined using the Bio-Rad (Mississauga, Ont.) Coomassie protein stain.

Immediately prior to use, microsomal preparations were thawed, subjected to a brief sonication, and then diluted to a protein concentration of 125 $\mu\text{g/mL}$ in 0.1 M Tris-HCl, 10 mM EDTA, pH 7.4, containing 0.5 mM phenol, 1 mM reduced glutathione, and 1 μM haematin. Compounds were tested at 8 concentrations in duplicate using 3-fold serial dilutions in DMSO of the highest drug concentration. A 5- μL sample of test compound or DMSO vehicle was added to 20 μL of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, in a 96-well polypropylene minitube plate (Beckman, Mississauga, Ont.) and mixed with 200 μL of the microsomal suspension. After a preincubation for 15 min at room temperature, 25 μL of a solution of 1 mM peroxide-free arachidonic acid (Cayman Chemical Co.) in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, was added to give a final concentration of arachidonic acid of 0.1 μM . The samples were mixed and incubated at room temperature for 40 min. Control samples contained ethanol vehicle instead of arachidonic acid. Following the incubation period, the reaction was terminated by the addition of 25 μL of 1 M HCl. Samples were neutralized by the addition of 25 μL of 1 M NaOH prior to quantitation of PGE_2 by radioimmunoassay (NEN-DuPont, Boston, Mass., or Amersham, Oakville, Ont.). These procedures were automated using a Biomek 1000 (Beckman). Cyclooxygenase activity in the absence of test compounds is defined as the difference between PGE_2 levels in samples incubated in the presence of arachidonic acid versus the ethanol vehicle. The percentage of inhibition of PGE_2 synthesis is calculated from the difference between PGE_2 levels in samples incubated in the absence or presence of the test compounds.

Thromboxane B_2 production by calcium ionophore activated human platelets

Platelets were prepared from human venous blood obtained from healthy volunteers. The collected blood was immediately mixed with 1/10th volume of anticoagulant solution (65 mM citric acid, 85 mM sodium citrate, and 2% glucose) and centrifuged at $200 \times g$ for 10 min. The supernatant was mixed with 50% volume of Hanks' balanced salt solution buffered with 15 mM Hepes, pH 7.4 (HHBSS), and 30% volume of the anticoagulant solution. This mixture was centrifuged at $750 \times g$ for 10 min, and the pellet was resuspended in HHBSS. Platelet concentration was determined with a Coulter counter. Platelets were preincubated at a final concentration of 4×10^7 cells/mL (0.2–0.25 mL) in the absence or presence of the inhibitor (from a 125-fold concentrated solution in DMSO) for 15 min before stimulation with 2 μM calcium ionophore A23187. After a further 10-min incubation at 37°C , cold (4°C) methanol was added (50% by volume) to stop the reaction and thromboxane B_2 (TXB_2) levels were measured by enzyme immunoassay (Assay Designs Inc.). Inhibitors were tested at 8 concentrations using 3-fold serial dilutions of the highest drug concentration. Human platelets released 13–20 ng of $\text{TXB}_2/10^7$ cells following challenge with 2 μM A23187 and 4–10 ng $\text{TXB}_2/10^7$ cells when stimulated with 1 μM arachidonic acid instead of ionophore. Less than 5% of the total production of TXB_2 was observed in the absence of ionophore challenge.

Assays with transfected CHO cells expressing COX-1

Stably transfected CHO cells expressing human COX-1 were obtained from G.P. O'Neill (Merck Frosst). The production of PGE_2 by the CHO[COX-1] cells following stimulation by arachidonic acid was used as a cell-based assay for COX-1 as previously described (Kargman et al. 1996b) and as summarized below. CHO[COX-1]

cells were washed once and resuspended in Hanks' balanced salts solution containing 15 mM Hepes, pH 7.4, at a cell concentration of 1.5×10^6 cells/mL. The cells were preincubated with test drug or DMSO vehicle for 15 min at 37°C before challenge with a final concentration of 0.5 μM arachidonic acid. After an incubation of 15 min at 37°C with arachidonic acid, the reaction was terminated by acidification. PGE_2 production was quantitated using an EIA (Correlate PGE_2 enzyme immunoassay kit, Assay Designs Inc., Ann Arbor, Mich.) or RIA (Amersham). The levels of PGE_2 in samples from CHO[COX-1] increased from <80 pg to 0.3–1.3 ng $\text{PGE}_2/10^6$ cells following stimulation with 0.5 μM exogenous arachidonic acid. Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE_2 levels of cells challenged with arachidonic acid versus the PGE_2 levels in cells mock challenged with ethanol vehicle. Each experiment included a set of 8 positive and negative control samples (\pm arachidonic acid challenge) for cells preincubated in the absence of inhibitor. Compounds were typically tested at 8 concentrations in duplicate using 3-fold serial dilutions in DMSO. Inhibition of PGE_2 synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

Results

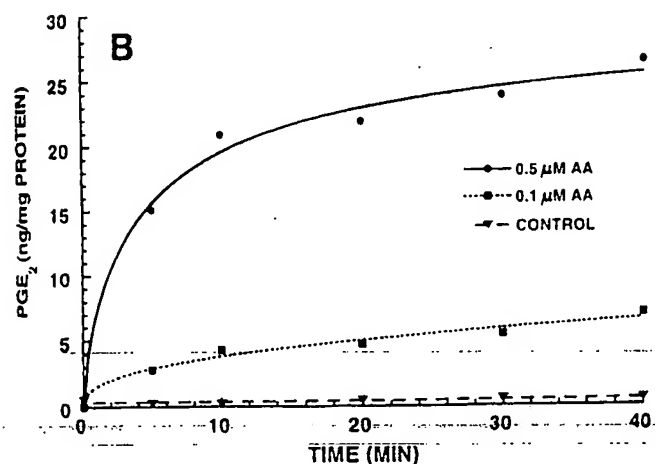
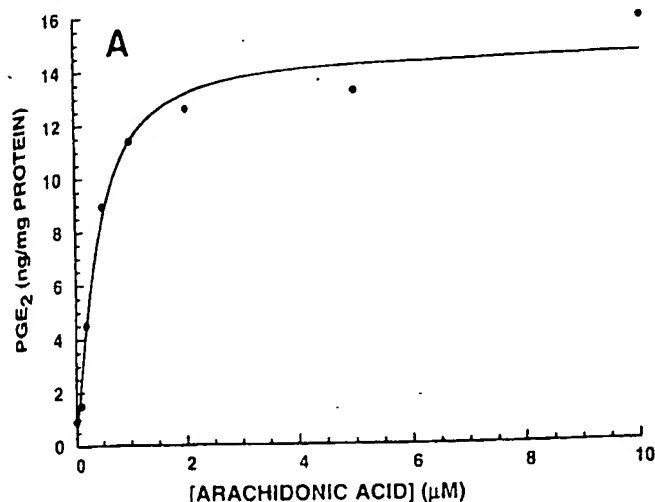
Measurement of COX-1 activity at low arachidonic acid concentration

Microsomal membranes from U937 cells were used as a source of COX-1 and assayed for the arachidonic acid dependent production of PGE_2 . The apparent K_m for arachidonic acid using this preparation was 0.6 μM (Fig. 1A). A significant stimulation of PGE_2 production was observed at the low concentrations of 0.1 and 0.5 μM arachidonic acid for which the time course of the reaction was measured over a 40 min period (Fig. 1B). An accumulation ranging from 3 to 12 ng PGE_2/mg protein for various preparations and an average 10-fold stimulation by arachidonic acid were measured using the 40-min reaction at 0.1 μM arachidonic acid. These conditions were selected for the evaluation of the inhibitory effects of compounds on the COX-1 reaction at a subsaturating concentration of arachidonic acid.

Effects of NSAIDs and COX-2 inhibitors on COX-1 activity assayed at low substrate concentration

The production of PGE_2 in the U937 microsome assay at low arachidonic acid can be inhibited dose dependently by NSAIDs and selective COX-2 inhibitors. Examples of inhibitor titrations showing that the nonselective flurbiprofen is about 300 and 10 000 times more potent at inhibiting microsomal COX-1 than the selective COX-2 inhibitors NS-398 and DFU, respectively, are given in Fig. 2. The inhibition by flurbiprofen was stereoselective, the (*S*)-flurbiprofen being 600-fold more potent than (*R*)-flurbiprofen (Table 1). The assay was very sensitive to inhibition and allowed the detection of inhibitory effects for each of the NSAIDs and selective COX-2 inhibitors tested (Table 1). IC_{50} values ranged from 0.6 nM for (*S*)-flurbiprofen to 500 μM for salicylic acid. L-745,296, a selective COX-1 inhibitor (Leblanc et al. 1995), was a very potent inhibitor of COX-1 under these conditions, with an IC_{50} value of 1.9 nM. The selective COX-2 inhibitors NS-398 (IC_{50} 0.3 μM), SC-58125 (IC_{50} 0.76 μM), L-745,337 (IC_{50} 2.8 μM), and DFU (IC_{50} 13 μM) were, respectively, 15-, 38-, 140-, and 640-fold less potent inhibitors of the microsomal COX-1 activity at low

Fig. 1. Production of PGE₂ by microsomes from U937 cells. (A) Dependence of PGE₂ production on arachidonic acid concentration, using a reaction time of 3 min. (B) Time dependence of the production of PGE₂, using initial arachidonic acid concentrations of 0.1 and 0.5 μ M.



arachidonic acid concentration than indomethacin (IC₅₀ 20 nM).

Inhibition of TXB₂ production by human platelets

The potency of NSAIDs and COX-2 inhibitors as inhibitors of Ca²⁺ ionophore induced TXB₂ production by human platelets was also determined (Table 1). Potent time-dependent inhibitors, such as flurbiprofen and indomethacin, showed IC₅₀ values in the low nanomolar range, which is similar or slightly lower than those measured using the U937 microsomal assay. For selective COX-2 inhibitors such as DuP 697, NS-398, and DFU, which behave as reversible competitive inhibitors of COX-1, IC₅₀ values were in general 2–10 times higher in the platelet than in the microsomal assay. A good correlation was observed between the IC₅₀ values measured for the inhibition of PGE₂ production by microsomes at low arachidonic acid concentration and those determined for the inhibition of TXB₂ by calcium ionophore stimulated platelets (Fig. 3). Some deviation was observed with flufenamic acid and etodolac, which were found to be either less or more potent, respectively, in the

Fig. 2. Concentration dependence of the inhibitory effects of NSAIDs and COX-2 inhibitors on the production of PGE₂ by U937 microsomes. Inhibitors were preincubated with the enzyme for 15 min prior to incubation for 40 min with 0.1 μ M arachidonic acid.

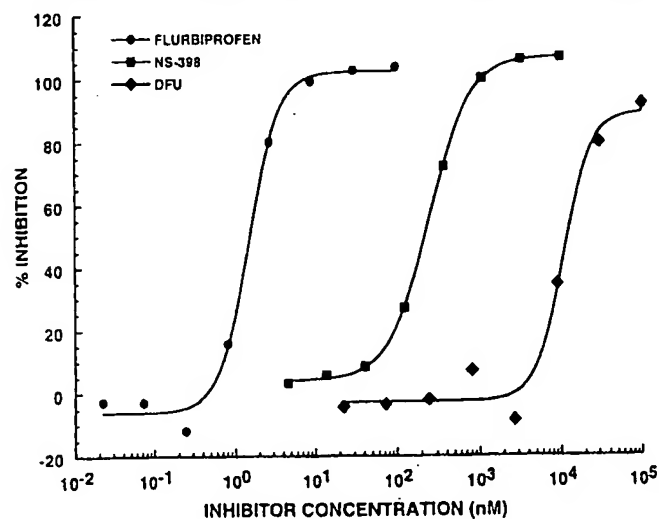
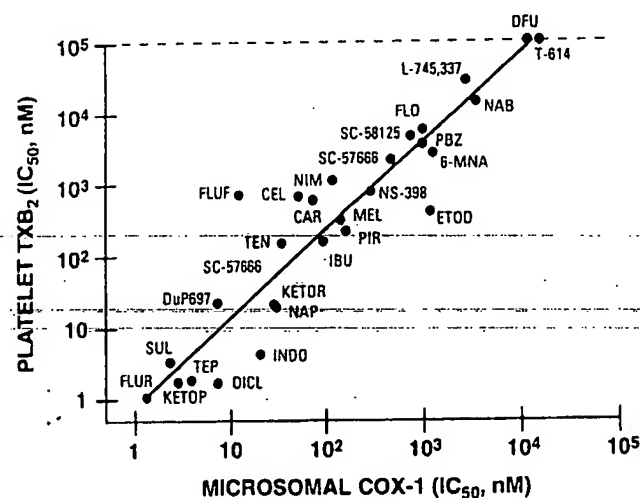


Fig. 3. Correlation between the IC₅₀ values of the platelet and microsomal assays for COX-1. Compounds were tested for the inhibition of TXB₂ by calcium ionophore stimulated platelets and for inhibition of the production of PGE₂ by U937 microsomes at low substrate concentration. Data for the different NSAIDs and COX-2 inhibitor are from Table 1.

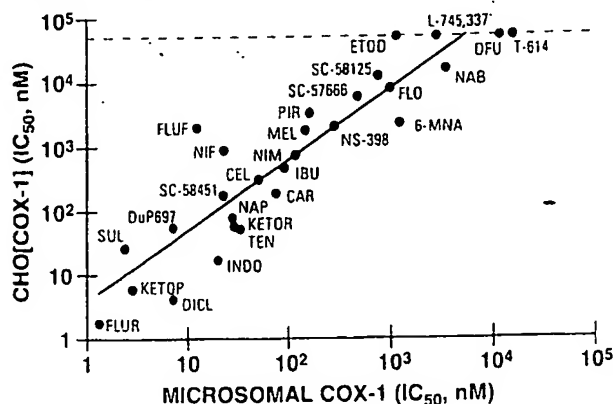


platelet assay than inhibitors of comparable potency in the COX-1 microsomal assay. The results suggest that the inhibition of COX-1 accounts for the effects of most of the inhibitors tested on TXB₂ synthesis by activated platelets.

Inhibition of PGE₂ production by CHO[COX-1] cells

The production of PGE₂ by CHO[COX-1] cells stimulated by arachidonic acid (0.5 μ M) has been used previously as a cell-based assay for COX-1 (Kargman et al. 1996b). Comparison of the inhibition data obtained for the CHO[COX-1] cells with those of ionophore-challenged platelets (Table 1) indicates that certain inhibitors are more potent in the latter assay, with the largest differences observed for piroxicam and etodolac (16- and 120-fold, respectively). In general, the rank order of potency of the various inhibitors tested was similar to that of

Fig. 4. Correlation between the IC_{50} values for the inhibition of PGE_2 in the CHO[COX-1] cells and microsomal COX-1 assays. Data are from Table 1.



the other two assays for COX-1. The correlation between the IC_{50} values for the CHO[COX-1] and U937 microsomal assays is shown in Fig. 4.

Discussion

Several factors have been implicated in the mechanism of gastrointestinal intolerance to NSAIDs, including topical irritation, promotion of acid back-diffusion into the gastric mucosa, enterohepatic recirculation, uncoupling of oxidative phosphorylation, and inhibition of the synthesis of cytoprotective prostaglandins (Hudson et al. 1992; Whittle 1992). Prostaglandins of the gastrointestinal tract are mainly derived from COX-1 (Kargman et al. 1996a) and appear to protect the gastric mucosa by inhibiting acid secretion, raising bicarbonate output and mucous secretion, and by maintaining mucosal blood flow (Appleyard et al. 1996; Polissou 1996; Wallace 1994). There has been some discussion about the relative importance of the various mechanisms, but most investigators seem to regard the mechanism of NSAID toxicity as a multifactorial process, of which COX-1 inhibition is one important element (Bennett and Tavares 1995; Hayllar and Bjarnason 1995; Wallace 1994). The multiplicity of the factors involved in mucosal cytoprotection might also explain the absence of spontaneous gastrointestinal lesions in COX-1-deficient mice (Langenbach et al. 1995).

To develop a sensitive assay for the inhibition of COX-1, we have optimized an assay at low arachidonic acid concentration, using microsomes from U937 cells. This assay was found to be more reproducible and slightly more sensitive than that using the purified enzyme at the same arachidonic acid concentration, presumably as a result of membranes acting as a carrier and further diluting the arachidonic acid substrate. It was more sensitive to inhibition than assays using gastric mucosa homogenates (Boughton-Smith and Whittle 1983) or minced intestinal tissues (Futaki et al. 1992). The evaluation of inhibitory effects on COX-1 at low arachidonic acid may be especially relevant to those related to NSAID-induced gastropathy considering that the utilisation of arachidonic acid appears to be limiting in the gastric mucosa. For example, the intragastric administration of arachidonic acid has been shown to cause a 400-fold elevation of PGE_2 over basal levels (Doyle et al. 1989). In addition, the presence of arachidonic acid binding proteins, which reduce arachidonic acid utilisation by cy-

cloxygenase, has been demonstrated in microsomes from the gastric mucosa (Preclik et al. 1992).

It should be noted that the effect of lowering the arachidonic acid concentration on inhibitory potency will depend on the mechanism of inhibition of the particular compound tested. Three different mechanisms of inhibition have been elucidated for COX-1 inhibition (Griswold and Adams 1996). A first mechanism of inhibition involves the time-dependent formation of a tight enzyme-inhibitor complex and is typically observed for potent nonselective inhibitors such as indomethacin and flurbiprofen. The second mechanism is through a rapid reversible binding to the enzyme, competitive with arachidonic acid. Less potent inhibitors of COX-1, such as the selective COX-2 inhibitors DuP 697, NS-398, and DFU, fall into this category. Acetylsalicylic acid has a distinct irreversible mechanism involving a covalent acetylation of an active-site serine residue. In assays where inhibitors are preincubated with enzyme prior to the addition of arachidonic acid, lowering the substrate concentration will result in an increase in potency for competitive inhibitors, whereas little effect should be observed for slowly reversible and irreversible inhibitors.

A good correlation was found between the inhibition of microsomal COX-1 and both the inhibition of TXB_2 synthesis by Ca^{2+} ionophore challenged platelets and the inhibition of PGE_2 production by CHO[COX-1] cells. The IC_{50} values in the platelet assay are about 10- to 300-fold lower than those reported for platelets stimulated with 5–10 μM arachidonic acid (Grossmann et al. 1995; Klein et al. 1994). The difference in potency might be explained by a higher effective concentration of arachidonic acid in the latter assay compared with ionophore-challenged platelets. In other experiments, we have observed a decrease in potency for several inhibitors by raising either the ionophore or arachidonic acid concentration (unpublished observations).

Long-term use of NSAIDs is associated with gastrointestinal side-effects such as ulceration and bleeding (Champion et al. 1997; Langman et al. 1994). All NSAIDs tested were found to inhibit the synthesis of COX-1-derived PGE_2 in the U937-microsome assay at low arachidonic acid concentration. The assay allows the discrimination of inhibitor potencies over a wide range of IC_{50} values, ranging from 1 nM for flunixin and flurbiprofen to 200–500 μM for salicylate and acetaminophen. The latter two compounds are also very weak inhibitors of gastric PGE_2 production in vivo, acetaminophen being non-ulcerogenic and salicylate having toxic effects on the gastric mucosa, which appears to be unrelated to the inhibition of prostanoid synthesis (Laporte et al. 1991; Whittle 1992). Acetylsalicylic acid was only slightly more potent than salicylate in the COX-1 microsomal assay. Acetylsalicylic acid is a known inhibitor of the production of gastric prostaglandins at high doses, and its potency was probably underestimated relative to other inhibitors under the present assay conditions, considering the irreversible mechanism of inhibition. Several of the currently marketed NSAIDs such as ketorolac, naproxen, piroxicam, nimesulide, and meloxicam had a potency similar to that of ibuprofen, with IC_{50} values 10 to 50 times higher than those of flurbiprofen, ketoprofen, or meclofenamic acid. Tepoxalin was among the most potent COX-1 inhibitors. The weak ulcerogenicity of this compound in rats has been related to dual inhibitory effects on the syntheses of prostaglandins and leukotrienes (Argentieri et al. 1994). Both the prod-

Table 1. Effects of NSAIDs and COX-2 inhibitors on COX-1 activity from U937 cell microsomes, human platelets, and CHO[COX-1] cells.

	IC ₅₀ (nM)		
	U937 microsomes	Platelets	CHO[COX-1]
(S)-Flurbiprofen	0.6 ± 0.2 (3)	nd	0.5 ± 0.3 (2)
Flunixin	1.1 ± 0.1 (2)	nd	17 ± 5 (2)
Flurbiprofen	1.4 ± 0.3 (3)	1.1 ± 0.1 (2)	1.8 ± 0.4 (7)
L-745,296	1.9 ± 0.4 (2)	nd	31 (1)
Sulindac sulfide	2.3 ± 0.9 (2)	3.3 ± 1.1 (3)	28.0 ± 6.7 (10)
Ketoprofen	2.8 ± 0.3 (3)	1.7 ± 0.1 (2)	6.1 ± 0.1 (2)
Meclofenamic acid	3.8 ± 0.4 (3)	nd	1.8 (1)
Tepoxalin	3.8 ± 0.4 (2)	1.8 ± 0.3 (2)	<22 (2)
Diclofenac	7.0 ± 3.0 (3)	1.7 ± 0.1 (2)	4.3 ± 1.1 (5)
DuP 697	7.1 ± 3.4 (3)	21.9 ± 5.9 (3)	59 ± 14 (8)
Flufenamic acid	12.1 ± 3.3 (3)	700 ± 330 (2)	2 100 ± 960 (10)
Indomethacin	19.8 ± 0.2 (23)	4.8 ± 1.1 (4)	17.6 ± 3.1 (7)
SC-58451	23.0 ± 1.6 (3)	nd	180 ± 110 (2)
Niflumic acid	23.3 ± 0.8 (3)	nd	950 ± 250 (4)
Zomepirac	24.2 ± 1.1 (3)	nd	nd
Ketorolac	28.0 ± 6.5 (3)	21.3 ± 9.9 (2)	82.9 ± 0.8 (3)
Mefenamic acid	28.8 ± 8.3 (2)	nd	nd
Naproxen	29.4 ± 7.5 (3)	19.7 ± 5.8 (3)	62 ± 29 (3)
Tolmetin	30.1 ± 3.3 (2)	19.5 ± 1.6 (2)	157 (1)
Tenidap	34 ± 13 (4)	144 ± 56 (3)	55 ± 27 (2)
Fenoprofen	47.1 ± 0.7 (2)	nd	nd
Celecoxib	52.3 ± 8.7 (3)	660 ± 20 (2)	320 ± 120 (2)
Carprofen	75.9 ± 2.0 (2)	610 ± 140 (4)	200 ± 120 (2)
Ibuprofen	94 ± 13 (3)	154 ± 3 (2)	470 ± 60 (8)
Nimesulide	117 ± 37 (3)	1 110 ± 440 (4)	780 ± 220 (3)
Meloxicam	143 ± 55 (2)	310 ± 110 (3)	1 810 ± 430 (4)
Piroxicam	163 ± 17 (3)	210 ± 130 (3)	3 460 ± 990 (4)
Tenoxicam	229 ± 71 (2)	nd	nd
RS-57067	287 ± 8 (2)	1 900 ± 400 (3)	3 580 ± 860 (2)
NS-398	300 ± 120 (4)	780 ± 310 (5)	1 930 ± 610 (12)
Fenclofenamic acid	316 ± 35 (3)	nd	nd
(R)-Flurbiprofen	390 ± 55 (3)	nd	620 (1)
SC-57666	480 ± 130 (3)	2 100 ± 200 (3)	6 000 ± 1 900 (2)
SC-58125	762 ± 68 (3)	4 800 ± 1 400 (3)	12 300 ± 8 700 (3)
Flosulfide	1 005 ± 70 (3)	6 000 ± 1 700 (4)	8 100 ± 3 700 (3)
Phenylbutazone	1 012 ± 77 (2)	3 700 ± 1 700 (4)	8 000 ± 1 800 (2)
BW 755C	1 010 ± 210 (3)	nd	nd
Etidolac	1 200 ± 260 (4)	400 ± 110 (3)	~50 000 (5)
6-MNA	1 300 ± 600 (6)	2 800 ± 1 800 (6)	2 290 ± 530 (4)
Isoxicam	1 320 ± 190 (2)	nd	4 200 (1)
L-745,337	2 780 ± 280 (3)	29 000 ± 19 000 (5)	~50 000 (5)
Nabumetone	3 530 ± 730 (3)	14 100 ± 5 500 (5)	15 700 ± 2 700 (2)
Azapropazone	3 800 ± 1 200 (4)	nd	nd
Benoxaprofen	3 840 ± 780 (2)	nd	nd
DFU	12 600 ± 2 400 (11)	> 100 000 (8)	> 50 000 (6)
T-614	16 700 ± 4 800 (4)	> 40 000 (3)	> 50 000 (2)
Sulindac sulfoxide	15 600 ± 5 100 (5)	nd	nd
Acetylsalicylic acid	21 500 ± 6 400 (3)	nd	nd
Sulindac sulfone	46 900 ± 7 800 (5)	nd	nd
Acetaminophen	188 000 ± 59 000 (3)	nd	~50 000 (2)
Salicylic acid	490 000 ± 120 000 (3)	nd	nd

Note: Compounds were tested using a 15-min preincubation in the indicated assay. IC₅₀ values are given ± range (n = 2) or SE (n > 2); nd, not determined.

nabumetone and its active metabolite 6-MNA (Blower 1992), a rather nonselective cyclooxygenase inhibitor (Grossmann et al. 1995), were found to inhibit the microsomal COX-1. Sulindac sulfone and sulindac sulfoxide also caused inhibition

at high concentrations but were considerably less potent than the active sulindac sulfide form.

Inhibition of COX-1 at low substrate concentration was detected with all selective COX-2 inhibitors tested, including

DuP 697, NS-398, SC-58125, and L-745,337, for which anti-inflammatory effects have been demonstrated at doses that are non-ulcerogenic and that do not inhibit gastric PGE₂ production (Chan et al. 1995; Futaki et al. 1994; Gans et al. 1990; Masferrer et al. 1994; Seibert et al. 1994). Among the compounds for which in vitro selectivity for COX-2 has been reported, the rank order of potency against COX-1 was DuP 697 > SC-58451 > celecoxib > nimesulide ~ meloxicam ~ piroxicam ~ NS-398 ~ RS-57067 > SC-57666 > SC-58125 > flosulide > etodolac > L-745,337 > DFU ~ T-614. For this class of compounds, it is expected that the selectivity ratio of COX-2/COX-1 inhibition will be of primary importance to determine the effective dose as anti-inflammatory and analgesic agent versus the dose responsible for gastrointestinal side effects. For example, T-614, which was found to be about 300-fold less potent than celecoxib in the COX-1 microsomal assay, is also about 100-fold less potent as a COX-2 inhibitor in the CHO[COX-2] assay (unpublished observations). Gastrointestinal toxicity has been observed at high doses with meloxicam, piroxicam, flosulide, and etodolac (Engelhardt et al. 1995; Melarange et al. 1995; Wiesenberger-Bottcher et al. 1989) and may be related to COX-1 inhibition. No detectable loss of the integrity of the gastrointestinal tract was observed with DFU administered at a dose 200-fold higher than the efficacious anti-inflammatory dose (Riendeau et al. 1997). Obviously, the ability of these inhibitors to block COX-1 activity in vivo will depend on a number of different factors, including oral bioavailability, tissue distribution, binding to protein, and pharmacokinetics. Therefore, the ulcerogenic potential of a compound cannot be predicted simply on the basis of its potency as an inhibitor of COX-1 in vitro. Nevertheless, the microsomal assay at low substrate concentration is particularly useful to compare relative potencies of weak inhibitors of COX-1.

Acknowledgments

The authors thank P. Roy, Y. Leblanc, P. Hamel, Z. Wang, Y. Gauthier, M. Thérien, J. Scheigetz, C. Black, C.S. Li, N. Ouimet, and P. Prasit of the Department of Medicinal Chemistry, Merck Frosst, for the synthesis of the various COX-2 inhibitors.

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Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen

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Abstract

Background—Selective inhibitors of cyclooxygenase (COX)-2 may provoke less gastric damage and platelet inhibition than conventional non-steroidal anti-inflammatory drugs.

Aims—We compared the biochemical and gastrointestinal effects of nimesulide, a potent and selective COX-2 inhibitor, with naproxen which exhibits no selectivity.

Subjects—Thirty six healthy volunteers were randomised to nimesulide 100 mg or naproxen 500 mg twice daily for two weeks in a double blind, crossover study with a washout between treatments.

Methods—Gastrointestinal side effects were assessed by endoscopy, and by estimation of small intestinal absorption-permeability and inflammation. Comparisons were made between variables at the end of each treatment phase.

Results—Nimesulide caused significantly less gastric injury using the modified Lanza score ($p < 0.001$) as well as reduced duodenum injury ($p = 0.039$). Nimesulide had lower visual analogue scores (VAS) for haemorrhage and erosive lesions in the stomach ($p < 0.001$) and for mucosal injection in the duodenum ($p = 0.039$). Naproxen increased excretion of calprotectin, a marker of intestinal inflammation (5.5 (1.2) to 12.1 (2.1) mg/l) while nimesulide had no effect (treatment difference $p = 0.03$). Naproxen abolished platelet aggregation to arachidonic acid and suppressed serum thromboxane B₂ (TXB₂) by 98%, indices of COX-1 activity. In contrast, nimesulide had no significant effect on platelet aggregation, although it reduced serum TXB₂ by 29%. Production of prostaglandin E₂ and prostacyclin by gastric biopsies, also COX-1 dependent, was inhibited by naproxen, but not by nimesulide. COX-2 activity, determined as endotoxin induced prostaglandin E₂ formation in plasma, was markedly suppressed by both treatments.

Interpretation—Nimesulide has preferential selectivity for COX-2 over COX-1 in vivo at full therapeutic doses and induces less gastrointestinal damage than that seen with naproxen in the short term.

(Gut 2001;48:339-346)

Keywords: cyclooxygenase; prostaglandins; platelet aggregation; non-steroidal anti-inflammatory drug enteropathy

Non-steroidal anti-inflammatory drugs (NSAIDs) are a major cause of iatrogenic gastrointestinal injury.¹⁻⁶ Gastrointestinal toxicity is particularly evident in the stomach² and duodenum,⁷ although injury occurs throughout the bowel.⁸ Cross sectional endoscopic studies in patients receiving NSAIDs show an ulcer prevalence of 10-25% with significant attendant mortality and morbidity.⁸⁻⁹ NSAIDs may also injure the small intestine, leading to a spectrum of damage from a change in permeability through to inflammation and ulceration, which may lead to anaemia¹⁰ and occasionally stricture formation.¹¹

NSAIDs are inhibitors of cyclooxygenase (COX) and prostaglandin (PG) formation. Two isoforms of the enzyme have been identified, COX-1¹² which is present in most cells, and COX-2¹³ which is largely absent in normal tissue but is inducible by cytokines, growth factors, and hormones,¹⁴⁻¹⁶ and is expressed at the site of inflammation.¹⁷ COX-1 is largely responsible for PG formation in the stomach and duodenum,^{18,19} although COX-2 expression has been reported. COX-1 is the only form of the enzyme found in platelets. Inhibition of COX-1 in the stomach, where the major product is PGE₂,¹⁹ may be responsible in part for the injury seen with NSAIDs.⁶ Moreover, in experimental models, selective inhibition of COX-2 is associated with minimal or no gastrointestinal damage.²⁰ Concomitant inhibition of COX-1 in platelets may also contribute to the haemorrhagic complications of gastrointestinal damage as this inhibits platelet thromboxane (TX) formation and aggregation, and prolongs bleeding time.^{21,22}

The majority of currently available NSAIDs inhibit both isoforms of the enzyme to a similar extent.²³ An important development has been the identification of several compounds with selectivity towards COX-2.^{24,25} These compounds offer the potential for suppressing COX-2 at sites of inflammation while preserving COX-1 in the stomach and platelets. Consequently, COX-2 inhibitors may induce less gastric injury and haemostatic impairment. Here, we compare the gastrointestinal tolerability and in vivo biochemical selectivity of nimesulide, a relatively selective inhibitor of

Abbreviations used in this paper: NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; PG, prostaglandin; TX, thromboxane; VAS, visual analogue score; LPS, lipopolysaccharide; PGI₂, prostacyclin; ADP, adenosine diphosphate; TRAP, thrombin receptor activator peptide.

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Accepted for publication
25 September 2000

COX-2^{26, 27} in vitro, with the non-selective COX inhibitor naproxen.

Subjects and methods

SUBJECTS

Thirty six healthy volunteers, aged 40–67 years, were recruited from two centres, Beaumont Hospital Dublin, Ireland (n=13) and University Hospital Reykjavik, Iceland (n=23). Specific exclusion criteria were a past history of intolerance to NSAIDs, modified Lanza score of >1 at baseline endoscopy, past history of peptic ulcer disease, or any other clinically significant medical disorder. The ethics committees of the participating hospitals approved the study protocol and written informed consent was obtained from all subjects.

STUDY DESIGN

At the start of period 1, subjects were randomly assigned to receive naproxen 500 mg twice daily and nimesulide placebo or nimesulide 100 mg twice daily and naproxen placebo for two weeks. The first period was followed by a two week washout and then subjects were assigned to the alternate therapies. The randomisation list was prepared using the software Rancode, v 3.1 (Gauting, Germany).

GASTRODUODENAL EVALUATION

Endoscopic evaluation of subjects was performed at the start and end of each period. Gastric and duodenal damage was assessed separately using a modified Lanza score²⁸ (tables 1, 2) and visual analogue score (VAS).²⁹ For the Lanza score, a score of 0 indicated no lesion, a single erosion or submucosal haemorrhage was given a score of 1, 2–10 erosions or submucosal haemorrhages a score of 2, >10 erosions or submucosal haemorrhages a score of 3, and an ulcer a score of 4. Lanza score 4 ("ulcer") required an excavated mucosal break of 5 mm or more. For VAS scoring, the severity of two parameters, haemorrhagic and erosive lesions in the stomach and duodenum, was assessed along a linear 150 mm scale. Haemorrhagic lesions ranged from the presence of a few single petechiae to profuse bleeding in the stomach or duodenum, and erosive lesions from one erosion to frank ulceration.

The washout period was extended for up to four weeks if gastroduodenal damage had not returned to normal by the beginning of period 2. At each endoscopy, the presence of *Helicobacter pylori* was determined by the rapid urease activity assay (CLO-test) and in four biopsy specimens, two each from the antrum and corpus by histology. All samples were stained with haematoxylin and eosin, a cresyl fast violet stain for *H. pylori*, and Gomori's aldehyde fuchsin to identify intestinal metaplasia.

Gastritis was assessed according to a modified Sydney system³⁰ which consists of a simple scoring system: absent=0, minimal=1, mild=2, moderate=3, and severe=4. The parameters scored were those associated with *H. pylori*, chronic inflammation, acute inflammation, atrophy, and metaplasia. The highest possible total score was 20 for the antrum or corpus, but any score above 0 was regarded as abnormal.

Reactive or chemical gastritis is associated with the use of NSAIDs. Parameters indicative of these changes were also documented and scored as follows: foveolar hyperplasia, arborisation of the muscularis into the mucosa, oedema, hyperaemia, paucity of inflammation, and atrophy. The maximum score was 24 for the antrum and corpus. A score of 6 or less was considered insignificant.

INTESTINAL ABSORPTION-PERMEABILITY

The 23 subjects from Iceland underwent a combined absorption-permeability test two days prior to and on day 10 of both the nimesulide and naproxen treatment periods, one hour following drug ingestion.³¹ All subjects abstained from alcohol and any medicines known to influence permeability and absorption. After an overnight fast, a test solution (100 ml of 3-*o*-methyl-D-glucose (0.2 g), D-xylose (0.5 g), L-rhamnose (1.0 g), and lactulose (5.0 g)) was administered orally and urine collected over five hours into 1 ml of 10% mercurithiosalicylate as preservative. Urinary sugars were determined by thin layer chromatography and scanning densitometry.³² The assay is sensitive, has 95% recovery, and a coefficient of variation of 2–8%.^{33, 34}

This test assesses several small intestinal transcellular functions and paracellular integrity. 3-*o*-Methyl-D-glucose is absorbed by active carrier mediated process, D-xylose by a passive carrier mediated process, and L-rhamnose by a non-mediated transcellular transport system. Lactulose on the other hand permeates selectively across the paracellular junctions of the adjacent enterocytes.^{31, 35} The differential urinary excretion of lactulose /L-rhamnose provides a specific index of intestinal permeability (intestinal barrier function). This permeability index is quite specific for mucosal function and is not significantly altered by pre-(gastric and intestinal dilution, gastric emptying, bacterial degeneration, etc) or post-(volume of distribution, renal function, etc) mucosal factors that can effect urinary excretion of these markers following ingestion.^{31, 35}

INTESTINAL INFLAMMATION

Twenty three subjects in Iceland provided a stool specimen for measurement of calprotectin concentration (a non-degraded, neutrophil specific marker) on the same day as the intestinal absorption-permeability test. Samples of stool (20 g) were frozen and stored at –20°C. After thawing, 5 g aliquots were suspended in 10 ml of faecal extraction buffer (Tris buffered isotonic (150 mM), saline, 10 mM CaCl₂, and 0.25 mM thiomersal as antimicrobial agent, pH 8.4) and homogenised for one minute with an Ultra Turrax (Ika Werke, Germany) mechanical homogeniser. The homogenates were centrifuged at 10 000 g at +4°C. The top halves of the supernatants were pipetted off, frozen, and stored at –20°C until quantitation by ELISA.^{36, 37}

The normal range of faecal calprotectin excretion and concentration was established in 53 healthy volunteers (30 males, median age 36 years (range 18–60)) and in 36 patients with

irritable bowel syndrome (10 men, median age 34 years (range 28–54)). Normal median calprotectin concentration was 3 mg/l with an upper limit (98% confidence limit) of 11 mg/l.

EFFECT OF DRUGS ON COX-1 AND COX-2 ACTIVITY

The effect of nimesulide and naproxen on COX-1 and COX-2 was assessed by several methods. Platelet aggregation and gastric mucosal PG generation were assessed in 13 Irish volunteers as a parameter of a COX-1 dependent process both before and during treatment with nimesulide and naproxen. In all 36 subjects, serum TXB₂ (reflecting COX-1 activity)²⁵ and lipopolysaccharide (LPS) induced PGE₂ synthesis (reflecting COX-2 activity)³⁸ in whole blood was measured both before and during treatment with nimesulide and naproxen.

GASTRIC MUCOSAL PROSTANOID SYNTHESIS

Prior to and on day 15 of treatment with nimesulide and naproxen in the 13 volunteers studied in Ireland, antral mucosal biopsies were obtained for determination of PGs (PGE₂ and 6-keto PGF_{1α}, a metabolite of prostacyclin (PGI₂)). Antral biopsies were incubated at 37°C for 45 minutes in 250 µl of phosphate buffered saline and the supernatant stored at –20°C for subsequent analysis. PGE₂ was measured by enzyme immunoassay (EIA) (Assay Design, Ann Arbor, Michigan, USA). The lower limit of detection of this assay is 36.2 pg/ml and cross reactivity is PGE₁ 70% and PGE₃ 16.3%. Cross reactivity with other eicosanoids is negligible. PGI₂ was determined as its hydrolysis product, 6-keto-PGF_{1α} (Assay Design). The sensitivity of this method is 1.4 pg/ml, and the cross reactivity with 2,3 dinor 6-keto-PGF_{1α} is 4% and negligible with other compounds. After analysis, total protein in each biopsy tissue was assessed (Bio-Rad DC, Hertfordshire UK) and the PG generated expressed as ng/mg protein.

SERUM THROMBOXANE SYNTHESIS

For serum TXB₂, 5 ml blood samples were taken prior to treatment and on days 3, 10, and day 15, one hour after dosing, placed in non-siliconised glass tubes prewarmed to 37°C and incubated at this temperature for one hour. Serum was separated and stored at –20°C until analysis by EIA (Assay Design).²⁵ The sensitivity of this method is 8 pg/ml, while cross reactivity is 7.1% with 2,3-dinor-TXB₂ and negligible with other compounds.

PLATELET FUNCTION

Platelet aggregation was evaluated in 13 subjects. Blood was obtained in 3.2% sodium citrate (9:1 v/v) predose, and on days 3 and 10 of treatment, at a time (1–2 hours following the morning dose) corresponding to peak plasma drug levels. Samples were centrifuged at 190 g for 15 minutes to obtain platelet rich plasma and at 900 g for a further 10 minutes to obtain platelet poor plasma. Platelet aggregation was assessed by light transmission (BioData PAP 4, Malvern, Pennsylvania, USA) in response to arachidonic acid 0.33 mM (entirely TXA₂

dependent), adenosine diphosphate (ADP) 10 µM (partly TXA₂ dependent), and thrombin receptor activator peptide (TRAP) 20 µM (TXA₂ independent). The response was determined as maximum platelet aggregation at four minutes.

COX-2 INHIBITION

COX-2 activity was assessed by estimation of LPS induced PGE₂ formation in whole blood.³⁹ For analysis of PGE₂, 5 ml of whole blood were added to a tube containing a final concentration of aspirin 200 µM (to inactivate any COX activity) and LPS 1 µg/ml (to induce COX-2 expression) in water and incubated at 37°C for 24 hours. Samples were centrifuged for 10 minutes at 900 g and plasma stored at –20°C until analysed by ELISA (Assay Design), as described above.

PLASMA DRUG LEVELS

Plasma naproxen and nimesulide levels were determined one and two hours following administration of the last dose, corresponding to peak plasma drug levels. Plasma naproxen levels were determined by fluorometric detection following liquid-liquid extraction on the Merck-Hibar Lichrosorb RP18 using a mobile phase of 0.05 M phosphate pH 3 buffer, methanol, and acetonitrile acid (50/25/25 v/v/v). The limit of sensitivity was 0.5 µg/ml. Plasma nimesulide was determined by high performance liquid chromatography with UV detection. The limit of detection was 0.01 µg/ml.

STATISTICAL ANALYSIS

The sample size was determined for the primary outcome measure, the modified Lanza score. Based on the assumption that the Lanza score would increase above 1 in 65% of naproxen treated subjects and in 25% of those receiving nimesulide, a bimodal distribution for two paired group analysis was used to compute sample sizes. The rate of subjects giving different results in different periods (rate of switchers) was estimated by computing the probability of remaining normal (Lanza ≤1) on nimesulide and abnormal on naproxen and vice versa and was 57%. Using a two sided test difference, we estimated that at least 29 subjects would be required (α=0.05, β=0.1). Statistical analysis was on a per protocol basis as the design was crossover. A crossover analysis was performed taking in the baseline values and the final values for each period.

For the Lanza score data, two analyses were performed. A categorical analysis was performed where individuals were defined as normal (Lanza score ≤1) or abnormal (Lanza score >1). The number of subjects belonging to the four categories of possible (binomial) results (normal on naproxen but abnormal on nimesulide; normal on nimesulide but abnormal on naproxen; normal on both; abnormal on both) was assessed by the McNemar χ² test. In addition, the raw Lanza scores, VAS, and biochemical analyses were analysed using a Koch³⁹ test. Only the results from the analysis of treatment effects (which uses the Wilcoxon

matched pairs test) are presented here. As non-parametric tests have been used for statistical analysis, medians are presented throughout, although mean and standard errors are also presented for biochemical results. Friedman analysis for multiple comparisons within treatments has been used to identify changes from baseline for the naproxen and nimesulide groups separately.

Table 1 Gastric damage scores (modified Lanza score): comparison of treatment effects of nimesulide and naproxen, and comparison of responders (Lanza score 0, 1) and non-responders (Lanza score >1)

Lanza score*	Nimesulide					Total naproxen
	0	1	2	3	4	
Naproxen						
0	3	0	1	0	0	4 (11%)
1	2	0	0	0	0	2 (6%)
2	5	1	2	1	0	9 (26%)
3	8	3	5	0	0	16 (46%)
4	2	1	1	0	0	4 (11%)
Total nimesulide (%)	20 (57%)	5 (14%)	9 (26%)	1 (3%)	0 (0%)	35
Analysis of responders†						
	Nimesulide					
	Responder (0, 1)		Non-responder (2, 3, 4)			
Naproxen						
Responder		5		1		
Non-responder		20		9		

McNemar test: $p < 0.001$ (two sided).

*Modified Lanza score: 0, normal; 1, erosion or submucosal haemorrhage; 2, 2–10 erosions or submucosal haemorrhages; 3, >10 erosions or submucosal haemorrhage; 4, ulcer.

†Responder is a Lanza score of 0 or 1; a non-responder is a Lanza score of >1.

Table 2 Duodenal damage scores (modified Lanza score): comparison of treatment effects of nimesulide and naproxen, and comparison of responders (Lanza score 0, 1) and non-responders (Lanza score >1)

Lanza score*	Nimesulide					Total naproxen
	0	1	2	3	4	
Naproxen						
0	15	3	1	0	1	20 (57%)
1	3	0	0	0	0	4 (11%)
2	6	1	1	0	0	7 (20%)
3	3	0	0	0	0	3 (9%)
4	1	0	0	0	0	1 (3%)
Total nimesulide (%)	28 (80%)	4 (11%)	2 (6%)	0 (0%)	1 (3%)	35
Analysis of responders†						
	Nimesulide					
	Responder (0, 1)		Non-responder (2, 3, 4)			
Naproxen						
Responder		22		2		
Non-responder		10		1		

McNemar test: $p < 0.001$ (two sided).

*Modified Lanza score: 0, normal; 1, erosion or submucosal haemorrhage; 2, 2–10 erosions or submucosal haemorrhages; 3, >10 erosions or submucosal haemorrhage; 4, ulcer.

†Responder is a Lanza score of 0 or 1; a non-responder is a Lanza score of >1.

Table 3 Gastric and duodenal damage score (visual analogue score): comparison of treatment effects of nimesulide and naproxen (mean (SEM) and median)

Type	VAS	Nimesulide	Naproxen	Nap-Nim	p Value*
Stomach					
	Haemorrhage lesions	14.0 (3.8) [0]	40.6 (6.0) [50]	26.5 (6.5) [12]	<0.001
	Erosive lesions	9.2 (2.9) [0]	61.7 (7.8) [52]	52.5 (7.3) [51]	<0.001
	Mucosal injection	24.8 (4.2) [25]	47.9 (3.8) [48]	23.1 (5.2) [22]	<0.001
Duodenum					
	Haemorrhage lesions	5.3 (3.0) [0]	11.5 (4.3) [0]	6.2 (4.5) [0]	0.165
	Erosive lesions	5.5 (4.3) [0]	15.3 (5.7) [0]	8.9 (7.5) [0]	0.181
	Mucosal injection	9.2 (2.8) [0]	22.5 (3.9) [21]	13.3 (4.2) [1]	0.038

*Koch test for difference between nimesulide and naproxen.

Results

Twenty four males and 12 females were recruited from the two centres. Demographic details and outcome measures were similar for the two centres and hence data from the two sites are presented jointly. The average age of subjects was 48 years (range 39–67). One male subject developed severe gastric damage at the end of the first treatment period where he had received naproxen, and as there was persistent ulceration four weeks later he was withdrawn from the study. As statistical analyses for crossover designs require patients to attend for more than one treatment period, this patient was omitted from these statistical analyses. Unless otherwise stated, data from 35 patients have been used for analyses.

ENDOSCOPIC EVALUATION

The results of the grading of gastrointestinal damage on the modified Lanza scale are shown in tables 1 and 2. One subject in the nimesulide group developed multiple (>10) gastric erosions and a separate subject developed a duodenal ulcer. By comparison, in the naproxen group, 16 developed multiple gastric erosions, four developed a gastric ulcer, three developed multiple duodenal erosions, and one a duodenal ulcer. Considering the main variable (rate of responders), the McNemar χ^2 test (two sided) analyses of patients categorised as normal (Lanza score ≤ 1) or abnormal (Lanza score >1) showed that nimesulide was better tolerated than naproxen ($p < 0.001$ in the stomach and $p = 0.039$ in the duodenum). Examining the raw scores, the median treatment difference was -2 due to worse scores with naproxen. For the VAS (table 3, fig 1) of haemorrhagic lesions in the stomach, scores were greater (worse) with naproxen (median 50) compared with nimesulide (median 0). The difference between treatments was significant ($p < 0.001$, Koch test, two sided). A similar result was evident for erosive lesions in the stomach ($p < 0.001$), mucosal injection in the stomach ($p < 0.001$), and mucosal injection in the duodenum ($p = 0.038$). No treatment differences were evident when comparing haemorrhage or erosive lesions in the duodenum. Comparison of Lanza scores for duodenal mucosal damage showed no difference (both median scores were zero, as was the median treatment difference).

Histological examination of the gastric biopsies showed that 19 of the 36 analysed subjects were positive for *H. pylori* prior to the first treatment. This was found not to affect the baseline Lanza scores, as the mean stomach score (averaged over the results for both treatments) was similar regardless of *H. pylori* status (positive patients, mean 0.05 (0.05), median 0; negative patients, mean 0.29 (0.11), median 0). Moreover, the presence of *H. pylori* did not influence the response to treatment.

INTESTINAL ABSORPTION-PERMEABILITY AND INFLAMMATION

Table 4 shows the results of the combined absorption-permeability tests. Neither treatment altered the absorption parameters (uri-

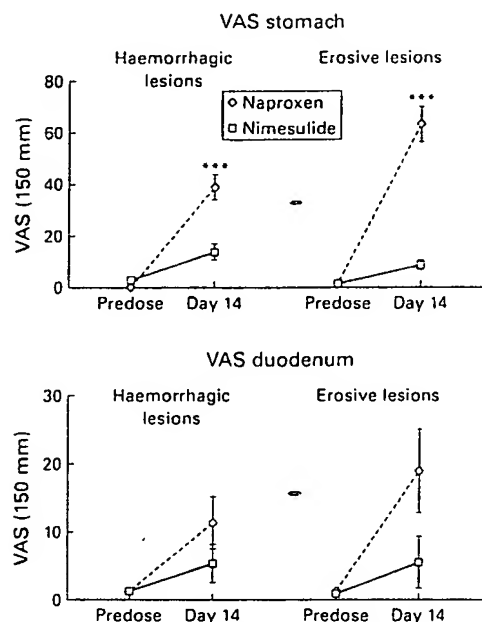


Figure 1 Comparison of the effects of nimesulide and naproxen on visual analogue scores (VAS) at endoscopy of the upper gastrointestinal tract before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). *** $p < 0.001$ between treatments.

nary excretion of 3-*o*-methyl-D-glucose, D-xylose, L-rhamnose). Naproxen increased intestinal permeability as reflected by an increase in the differential urinary excretion of lactulose/L-rhamnose, whereas nimesulide had no such effect; however, the treatment difference was not statistically significant on day 10.

INTESTINAL INFLAMMATION

Calprotectin concentration was determined in the faeces of 23 subjects as a marker of intestinal inflammation. The change from baseline to day 10 showed a significant treatment effect ($p = 0.03$): Nimesulide had no effect over the 10 days (6.1 (2.3) mg/l (range 0.5–55.0) *v* 6.9 (1.3) mg/l (range 0.5–25)) whereas naproxen increased calprotectin excretion (5.5 (1.2) mg/l (range 0–25) *v* 12.1 (2.1) mg/l (range 0–43)).

EICOSANOIDS GENERATION

PGE₂ and PGI₂ (measured as 6-keto PGF_{1α}) generation by gastric biopsy was similar to that reported previously.⁴⁰ Generation of both products was markedly reduced by naproxen but not by nimesulide and there was a significant difference between treatments ($p < 0.01$) (fig 2). Serum TXB₂ was markedly inhibited by naproxen, falling by 98% throughout the treatment period. For nimesulide, there was a small decrease from baseline to day 3

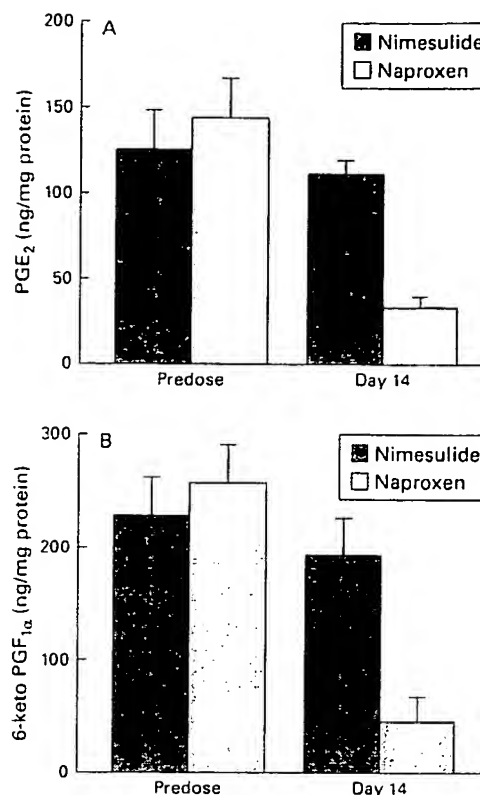


Figure 2 Comparison of the effects of nimesulide and naproxen on generation of prostaglandin (PG) E₂ (A) and 6-keto-PGF_{1α} (B) by gastric biopsies incubated at 37°C for 45 minutes before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). $p < 0.01$ between treatments.

(273 (13) *v* 180 (15) ng/ml) which resulted in an average decrease of 29% throughout the treatment period (treatment effect was $p < 0.001$ for the change from baseline to day 10) (fig 3A). LPS induced PGE₂ in plasma, which reflects COX-2 activity, was evaluated in 33 subjects. Plasma PGE₂ decreased by 74% on naproxen, less than the 93% reduction seen with nimesulide ($p = 0.053$ for the change from baseline to day 10) (fig 3B).

PLATELET AGGREGATION

A total of 13 patients were analysed for platelet aggregation, although due to missing data, values from 7 to 12 patients are available when changes from baseline are considered. Figure 4 shows that arachidonic acid induced platelet aggregation, which is dependent on COX-1 mediated TXA₂ formation, was largely unaffected by nimesulide. In contrast, there was marked suppression of arachidonic acid induced platelet aggregation throughout administration of naproxen. (Friedman analysis $p < 0.001$ on days 3, 10, and 15). Treatment

Table 4 Intestinal absorption and permeability before and after nimesulide and naproxen (mean (SEM) and [median]) ($n = 23$)

Test substance	Nimesulide		Naproxen		Nim-Nap	<i>p</i> Value*
	Baseline	Day 10	Baseline	Day 10	Day 10	
3- <i>o</i> -m-D-glucose (%)	46 (2.9) [45]	41 (2.2) [44]	46 (2.2) [47]	41 (2.4) [42]	-0.0 (2.8) [-1.2]	0.8328
D-xylose (%)	28 (1.5) [28]	27 (1.2) [26]	29 (1.3) [30]	27 (1.6) [28]	-0.4 (2.0) [-2.8]	0.9410
L-rhamnose (%)	8.4 (0.5) [8.5]	8.0 (0.4) [8.0]	9.0 (0.7) [9.5]	8.8 (0.7) [8.4]	-0.8 (0.7) [-0.8]	0.5658
Lactulose/L-rhamnose	0.028 (0.0) [0.023]	0.027 (0.0) [0.029]	0.032 (0.01) [0.025]	0.042 (0.01) [0.034]	-0.015 (0.01)* [-0.007]	0.1070

*Koch test, treatment effect.

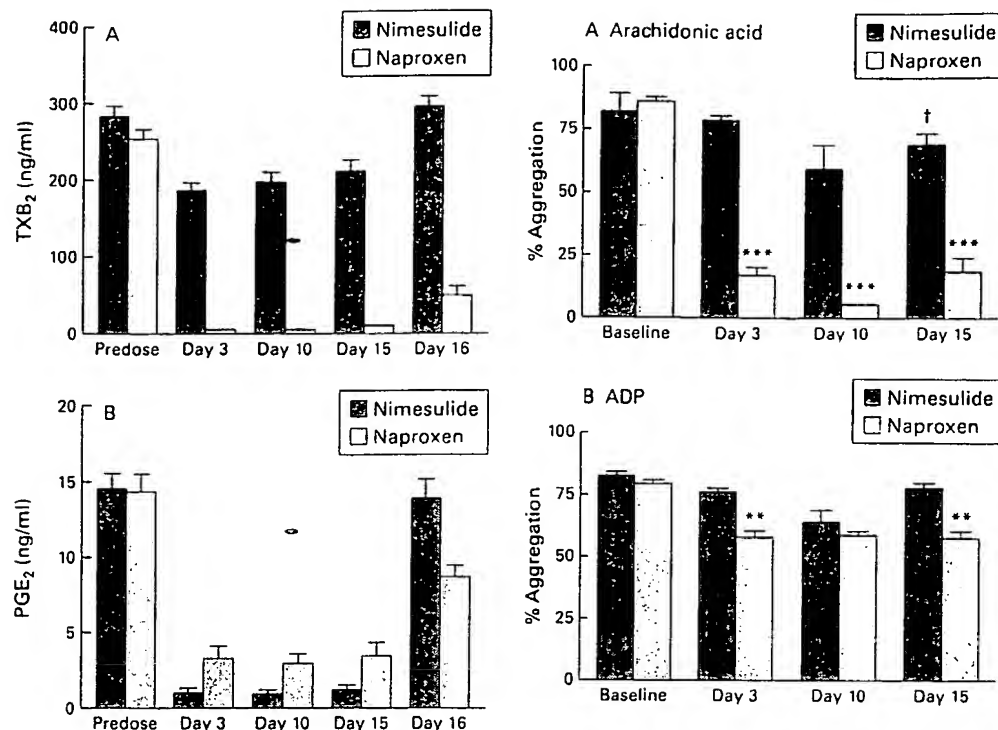


Figure 3 (A) Comparison of the effects of nimesulide and naproxen on serum thromboxane B₂ (TXB₂) (a measure of COX-1 activity) before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). Naproxen had a greater effect on serum TXB₂ ($p < 0.001$ for comparison between treatments to day 10). Note that nimesulide reduced serum TXB₂ on average by 29% from baseline ($p < 0.01$) and that both drugs markedly reduced plasma PGE₂. (B) Plasma prostaglandin (PG) E₂ (a measure of COX-2 activity). Nimesulide had a slightly greater effect on plasma PGE₂ ($p = 0.053$ for comparison between treatments to day 10).

differences (from baseline) were analysed on day 10 and showed a significant ($p = 0.048$) effect. Platelet aggregation to ADP, where the secondary wave of aggregation is TXA₂ dependent, was not significantly altered by nimesulide but was inhibited by naproxen ($p < 0.01$ days 3 and 15). No significant treatment differences were evident on day 10. Nimesulide had no effect on TRAP induced platelet aggregation, which is independent of TXA₂ formation. Similarly, TRAP induced platelet aggregation was largely unaffected by naproxen, although a small degree of inhibition was noted on day 15. No treatment difference was evident on day 10.

PLASMA LEVEL OF NIMESULIDE AND NAPROXEN

Following the last dose, plasma concentrations of nimesulide were 5.4 (0.4) (range 0.13–11.4) µg/ml at one hour and 5.5 (0.3) (range 3.1–8.2) µg/ml at two hours, falling to 4.2 (0.3) (range 1.2–7.8) at four hours. Corresponding naproxen plasma levels were 70 (4) (range 22–110), 86 (4) (range 20–127), and 6.4 (2) (range 18–91) µg/ml. Plasma concentrations fell to undetectable levels for both drugs within 48 hours of discontinuation.

Discussion

Gastric and small intestinal damage is common in short and long term users of NSAIDs. NSAID induced gastroduodenal ulceration is

Figure 4 Comparison of the effects of nimesulide and naproxen on platelet aggregation to arachidonic acid (A), adenosine diphosphate (ADP) (B), and thrombin receptor activator peptide (TRAP) (C) before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). ** $p < 0.01$, *** $p < 0.001$ for changes from baseline; fp = 0.048 for comparison between treatments.

associated with life threatening bleeding or perforation in an estimated 1 in 5000–20 000 prescriptions.⁴¹ NSAID induced enteropathy may manifest as iron deficiency anaemia, hypoalbuminaemia due to protein loss,¹⁰ and rarely as small and large intestinal strictures.⁴² The mechanism of NSAID induced injury is thought to reflect, at least in part, inhibition of cyclooxygenase and loss of cytoprotective prostaglandins, although a direct "topical effect" may also play a role.⁵

Here, we examined the degree of gastroduodenal and small intestinal injury with nimesulide, a relatively selective COX-2 inhibitor during short term administration of the drug. Short term studies are thought to over represent erosive damage by NSAIDs compared with long term studies. However, they are suitable for the purpose of examining the effect of inhibiting COX as they avoid the confounding effect of "adaptation" whereby the damaging effects of COX inhibition is over-

come in time. The range and prevalence of the gastroduodenal damage by naproxen was in keeping with that previously described.⁴³⁻⁴⁵ By comparison, gastric damage with nimesulide was significantly less and 71% of patients remained within Lanza 0-1. This degree of gastric tolerability was similar to that described with the highly selective COX-2 inhibitors celecoxib⁴⁶ and rofecoxib.⁴⁷

As reported previously⁴⁸ with NSAIDs,⁴⁴⁻⁴⁵ duodenal damage was less marked than gastric damage and again was significantly less with nimesulide than naproxen. Nevertheless, a duodenal ulcer was found in a single subject on nimesulide who was positive for *H. pylori*. Parenthetically, *H. pylori* infection had no synergistic effect on damage caused by either drug in this study although this has been reported previously.⁴⁸

Increased permeability of the small intestine has been documented with most conventional NSAIDs.⁵¹ In this study, nimesulide failed to alter intestinal permeability, in keeping with animal studies.⁴⁹ In contrast, naproxen increased intestinal permeability, as shown previously in humans.⁵⁰ To date, all NSAIDs that increase intestinal permeability are associated with a high prevalence (40-65%) of NSAID enteropathy, measured as excretion of calprotectin.⁵¹ Not surprisingly then, naproxen but not nimesulide increased intestinal inflammation. Although it has been suggested that inflammation may be delayed for six months,⁵² it has been reported earlier,⁵³ in keeping with our study.

The improved gastrointestinal tolerability of nimesulide is consistent with its relative COX-2 selectivity and maintenance of gastric prostaglandin formation. As a measure of gastric COX activity, we examined generation of PGs in gastric mucosal biopsies. Nimesulide did not alter formation of either PGE₂ or PGI₂ in the stomach. PGE₂ is the major product of gastric epithelial cells.¹⁹ However PGE₂ is also generated by platelets so that any inhibitory effect of an NSAID could be due to inhibition of platelets contaminating the biopsies. To address this issue, we measured 6-keto PGF_{1α}, a metabolite of PGI₂. PGI₂ is generated by nucleated cells, such as gastric epithelial and vascular endothelial cells.⁵⁴ Naproxen inhibited both products whereas nimesulide had little effect on gastric PGE₂ or 6-keto-PGF_{1α} at a time when there were substantial levels of the drug in blood.

Studies in whole blood allowed us to compare the relative selectivity of the two compounds for the COX isoforms. Serum TXB₂, a measure of COX-1 activity of platelets,²¹ is highly sensitive to inhibition as platelets are incapable of regenerating new enzyme. Nimesulide inhibited serum TXB₂ by about 30% over the period of the study, as has been reported with the highly selective COX-2 inhibitor celecoxib.⁵⁵ However, it is unlikely that this modest effect would alter haemostatic function, as very marked (>95%) inhibition of platelet COX-1 is required to suppress platelet aggregation.⁵⁶ Indeed, platelet aggregation to

arachidonic acid and ADP, which is TXA₂ dependent, was preserved.

As a marker of a COX-2 effect, we used an assay developed by Panaro and colleagues³⁸ in which COX-2 in monocytes is induced by LPS, resulting in PGE₂ formation. Both drugs suppressed PGE₂ formation resulting from LPS treatment. This relative selectivity of nimesulide for COX-2 demonstrated *in vivo* is consistent with the selectivity seen *in vitro* at peak plasma levels achieved (~18 μM and 98% protein bound).²⁷

In summary, nimesulide causes less endoscopic and functional evidence of gastrointestinal injury compared with naproxen. This is consistent with our findings showing that nimesulide is a selective COX-2 inhibitor *in vivo*, with little effect on haemostatic function or gastric prostaglandin formation. A critical issue is whether the short term endoscopic benefits seen with a selective COX-2 inhibitor such as nimesulide translate into a more long term benefit, particularly a reduction in bleeding and perforation. In addition, it remains to be seen if an anti-inflammatory effect will ensue from COX-2 inhibition alone, in that COX-1 has been implicated in some models of inflammation. Indeed, in a mouse model of inflammation, Wallace and colleagues reported a significant reduction in inflammation with nimesulide but only at doses that also inhibited COX-1.⁵⁷

This study was supported by a grant from Helsinn Healthcare SA.

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Anti-ischemic Effects of Nimesulide, a Cyclooxygenase-2 Inhibitor on the Ischemic Model of Rabbit Induced by Isoproterenol

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(Received January 23, 2006)

The objective was to devise an animal model of myocardial infarction (MI) against which cardioprotective drugs might be tested. We describe the effects of nimesulide, a COX-2 inhibitor with development and validation of such a model. The rabbit was chosen in preference to rodents because its heart and cardiac circulation more closely resemble those of human. Thus, the cardiovascular system of anaesthetized male rabbits, 1 to 1.5 kg ($n=11$), was stressed by a single bolus intravenous injection of isoprenaline (ISP), 65 mg/kg. The effects of the injection were followed for sixteen days and were evaluated in four ways: 1) measurements of creatinine kinase isozyme and troponin-I (TPI) in serum 2) Electrocardiographic (ECG) changes (ST elevation and Q wave development) 3) Cardiac histopathology observed in tissue sections of the isolated heart. The histopathological analysis showed that rabbit heart on 2nd day after ISP injection showed changes of coagulation necrosis. Day 4 total coagulation with the loss of nuclear and striation associated with heavy interstitial infiltrate of neutrophils was found. Day 8 after infarction showed collagen deposition with capillary channels in between the remaining islands of myocytes in the infarcted area. On the 16th day scarring was complete. Coronary perfusion rates (CPR) and heart rate (HR) of the infarcted and nimesulide (a COX-2 inhibitor) treated rabbits displayed significant improvement ($n=11$) on each corresponding day after infarction as compared to the infarcted and saline treated rabbits ($P<0.05$). All four indices revealed similarities with effects commonly associated with MI in humans.

Key words: Isoprenaline (ISP), Troponin I (TPI), Creatine Phosphokinase (CPK), Electrocardiography (ECG), Histopathology, Coronary perfusion rates (CPR)

INTRODUCTION

The development of cyclooxygenase-2 (COX-2) inhibitors as anti-inflammatory agents without gastric toxicity is based on the fact that COX-1 predominates in stomach yielding cytoprotective prostaglandin E₂ (PGE-2), while COX-2 is induced in inflammation, giving rise to pain, swelling and discomfort (Mukerjee, 2002). The fact that COX-2 is an inducible enzyme particularly associated with inflammation led to the development of selective COX-2 inhibitors that offer comparable efficacy and fewer unwanted side effects attributable to COX-1 inhibition,

gastric ulceration in particular (Bombardier *et al.*, 2000; Silverstein *et al.*, 2000). Gastrointestinal safety of selective COX-2 inhibitors, however, may come at the cost of increased cardiovascular events, as suggested by the VIGOR trial (Mukerjee *et al.*, 2001).

The available clinical data with COX-2 inhibitors pertaining to cardiovascular endpoints was summarized recently (Mukerjee *et al.*, 2001). This data suggests the risk of cardiovascular events associated with the use of COX-2 inhibitor when used for arthritis. Studies performed by Duffy *et al.* (1999) have defined the relative roles of vasodilator prostaglandins in patients with atherosclerosis. In these studies, vasodilator prostaglandins were demonstrated to mediate metabolic vasodilatation and flow-mediated vasodilatation in response to rapid cardiac pacing in patients with atherosclerosis (Duffy *et al.*, 1999). At the other extreme is the possibility that COX-2 antagonists may serve to improve vascular health and retard atherosclerosis.

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Studies have shown that COX-2 is widely expressed in atherosclerotic lesions and may colocalize with inducible nitric oxide synthase and nitrotyrosine within macrophages (Baker *et al.*, 1999). Some studies show that short-term treatment with the COX-2 specific inhibitor rofecoxib and the nonselective COX antagonist naproxen does not impair endothelium-dependent or -independent vascular function in healthy volunteers. However, the role of COX-2 during experimentally induced ischemia is still unclear. In the present investigation we studied the anti-ischemic effects of nimesulide-a COX-2 inhibitor, in rabbits subjected to isoproterenol (ISP), an important β agonist. In this model the acute phases of myocardial necrosis and repair mimicked those, which occurred in humans (Saeed *et al.*, 1998). We have used nimesulide as a COX-2 inhibitor in our study.

METHODS AND MATERIALS

Male rabbits 1 to 1.5 kg were housed for at least 7 days before an experiment in the Animal Unit of HEJ Research Institute of Chemistry, University of Karachi. They were fed a standard rabbit chow with water freely available *ad libitum*.

Rabbits were divided into three groups of ten animals each. One group consisted of normal rabbits, second group consisted of infarcted rabbits treated with saline and the third group consisted of infarcted rabbits that were treated with nimesulide (a COX-2 inhibitor). All infarcted rabbits received nimesulide 25 mg/kg or saline 0.5 mL every day, up to and including the day of sacrifice. Experiments were performed on day 2, 4, 8 and 16 post-infarction.

On day two of experiment after taking the electrocardiographic (ECG), the blood samples for enzyme assays were obtained from the marginal ear vein. The rabbits were sacrificed and hearts removed and used for histopathological studies. After Langendorff study, the hearts were subjected to histological studies.

Myocardial infarction (MI)

In the present study, MI was induced by a single, parenteral dose of beta-adrenergic agonist, ISP (65 mg/kg). For many years the main technique for producing MI in animals was to manually occlude with a silk suture the anterior descending coronary artery of the anesthetized rat. A recent method calls for a single large parenteral dose of the β -adrenergic agonist, isoproterenol. (Saeed *et al.*, 1998). The advantages of isoproterenol-induced infarction, which occurs as a result of intense inotropic and chronotropic actions of isoproterenol compared to physical occlusion of coronary artery, are;

(1) Production of experimental MI with β -adrenergic agonist

is by comparison, less invasive and accomplished without the complicating factor of general anesthesia.

- (2) No foreign body (suture) remains on or in the heart.
- (3) Reperfusion is possible after isoproterenol since there is no permanent overt occlusion.
- (4) Reported survival rates with isoproterenol are better than after vessel occlusion.

Enzyme levels

1. Troponin I (TPI) was analyzed using IMMULITE Turbo Troponin I Analyzer (Adams *et al.*, 1993). Samples were loaded on bar-coded sample cup and then placed onto a load platform. We then loaded the bar-coded test units. Pressed "GO" and the test units were conveyed to the analyzer for bar-coded identification and then moved on to a main incubation carousel. The pipetter added sample and reagent and the test units were incubated at 37°C at 16 minutes. The test units were shuttled to the spin/wash station, where bound and free labels were separated. Substrate was then added and the test units were then transferred to the luminometer chain. 10 minutes incubation at 37°C began which caused the signal to reach maximum limits. The photon count was measured with a photo amplifier tube.

2. Creatine phosphokinase (CPK) reagent was used to measure the CPK activity by an enzymatic rate method (Rosalki, 1967). The SYNTRON CX System automatically proportions the appropriate sample and reagent volumes into the cuvette. The ration used is one sample to 20 parts reagent. The system monitors the change in absorbance at 340 nanometers. This change in absorbance is directly proportional to the activity of CPK in the sample and is used by the SYNTRON CX system to calculate and express creatine phosphokinase activity. Similarly blood for CPK was also drawn at 0, 4, 10, 16 and 28 h after isoproterenol injection from the marginal ear vein of the rabbit.

Electrocardiography (ECG)

ECG was obtained using modified Einthoven system. One lead each placed over the right and left rib cage vs. an indifferent lead on the left lower leg. Lead I to record potentials across the thorax, positive on the left and negative on the right. Lead II from the right thorax to the left leg has a negative to positive polarity.

Histopathology

Rabbits were killed; chest cavities opened and hearts were removed. After carrying out the Langendorff experiment, hearts were fixed in 10% buffered formalin. After proper fixation, the hearts were measured, bisected and entirely submitted into two cassettes. Tissue processing

was done by routine methodology. After processing, the tissues were embedded in paraffin using the histocentre from Shenden. 3-5 μ m thick sections were cut by Microtom AS 325 from Shenden and stained with hematoxylin and eosin (H & E). Selected sections were stained with trichrome and interpreted under an Olympus BX 50 microscope.

Langendorff isolated heart preparation

Coronary perfusion rate (CPR) was measured using Langendorff isolated heart preparation (Langendorff, 1985). Rabbits were killed by cervical dislocation and heart removed rapidly and placed in oxygenated Krebs Hanslet Solution (KHS). The pericardium was removed; a segment of aorta left attached. Residual blood was removed by massaging the heart in KHS. The heart was then transferred to the Langendorff apparatus (Bioscience Kent, UK.) where it was tied to a glass cannula. KHS warmed at 37°C and bubbled with 95% oxygen and 5% carbon dioxide was passed from an elevated reservoir at a constant pressure of 60 cm of water. This pressure causes the aortic valve to close, but permits the perfusate to enter the coronary circulation. When perfusion established, the heart began to beat to beat spontaneously. We let the heart stabilize till the contractions became rhythmic (usually 30 minutes).

Statistical analysis was done using one-way ANOVA followed by Bonferroni test for selected pair of groups. Differences were considered significant when probability (p) was <0.05 .

RESULTS

The results of the enzymes levels are shown in Fig. 1A and 1B. To confirm that MI had occurred by ISP, blood for troponin I was drawn at 0, 4, 10, 16 and 28 h after ISP injection from the marginal ear vein of the rabbit. The

results with TPI and CPK obtained show a continuous increase in the serum level of the enzyme which is suggestive of MI. This confirmed that MI had taken place in the rabbits.

The results of ECG also demonstrate (Fig. 2) that MI had occurred. ECG taken after ISP injection showed ST wave elevation and development of Q wave was also found. These findings further confirmed that infarction had taken place in the rabbit heart.

Photomicrographs of the rabbit heart muscle on the 2nd day after ISP injection shows changes of coagulation necrosis (Fig. 3, day 2). Ischaemic myocytes with pyknosis of nuclei, shrunken eosinophilic cytoplasm and marginal contraction band necrosis is seen. On the 4th day, total coagulation necrosis with the loss of nuclei and striation was observed (Fig. 3, day 4). We also found heavy interstitial infiltrate of neutrophils. On the day eight, collagen deposition with capillary channels in-between the remaining islands of myocytes in the infarcted area and prominent fibrovascular reaction in margins are seen (Fig. 3, day 8). On the 16th day scarring was complete. We noted prominent scarring with scattered remaining darkly stained myocytes (Fig. 3, day 16). All these changes are similar to those take place in the human heart after an acute MI.

Coronary perfusion rate

We observed a steady decrease in CPR in infarcted rabbits as compared to the normal rabbits ($p<0.05$) on the day 2 after infarction (Fig. 4A). On day 4 of post-infarction, there was further drop in CPR which reached its maximum decline on day 8 of post-infarction (Fig. 4B and 4C). Following day 8 of post-infarction, CPR started to recover and values returned close to those of day 2, although still away from the values of the normal rabbits (Fig. 4D).

Infarcted rabbits were divided into two groups. One group was treated with saline on the day of infarction and

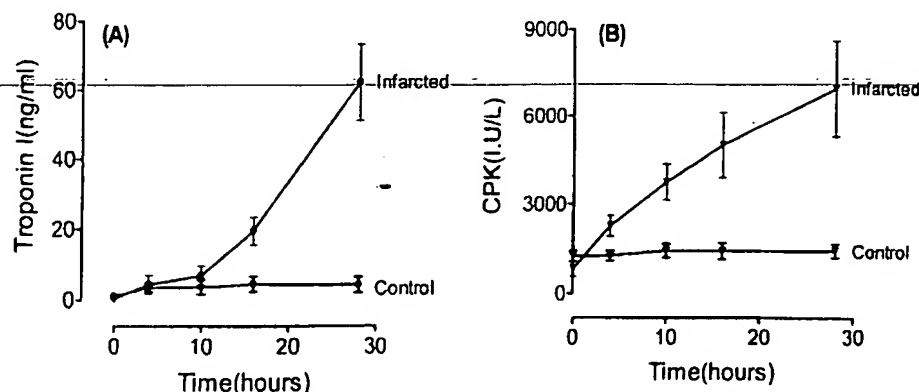


Fig. 1. (A) Troponin I levels in the blood at different time points after isoproterenol injection and (B) CPK levels in the blood at different time points after isoproterenol injection

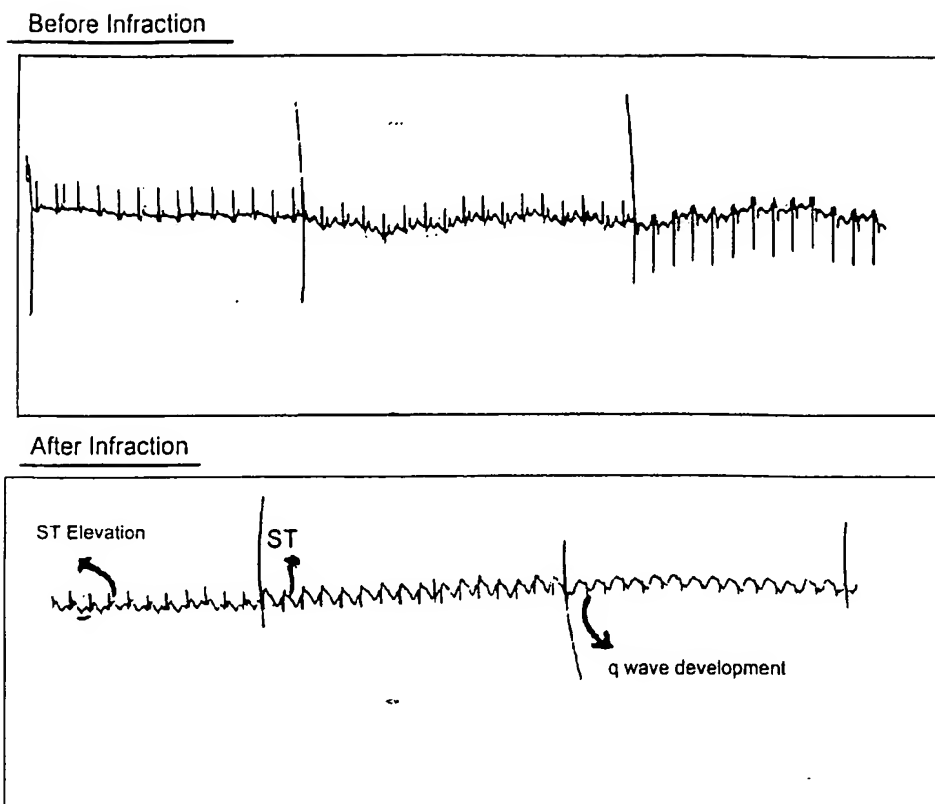


Fig. 2. ECG Tracings after Isoproterenol Injection

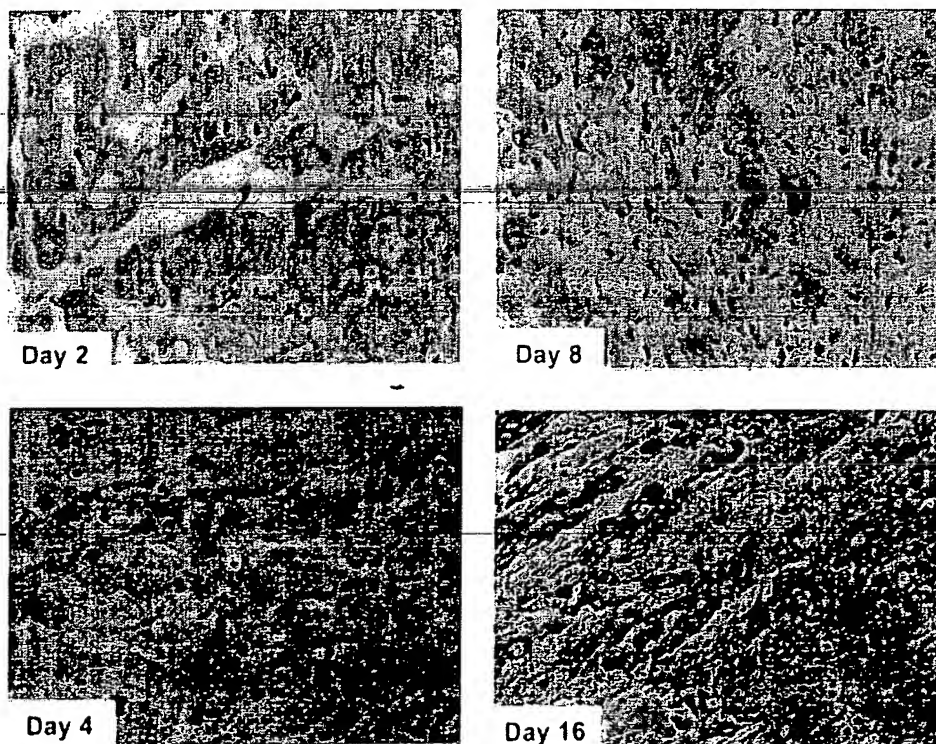


Fig. 3. Photomicrographs of the rabbit heart muscle (left ventricle), (day 2) after 24-28 hours of infarction. Ischemic myocytes show changes of coagulation necrosis. H & E. Magnification 20X (day 4) after 72-76 hours of infarction. Note florid predominantly acute inflammatory cell infiltrate around necrotic myocytes (arrow). H & E. Magnification 10X on day 8 after infarction. Note collagen deposition with capillary channels in-between the remaining islands of myocytes in the infarcted area (arrow). H & E. Magnification 10X (day 16) Photomicrograph of the rabbit heart muscle (left ventricle) on day 16 after infarction. Note prominent scarring with scattered remaining darkly stained (arrow myocytes. Trichrome Magnification 20X.

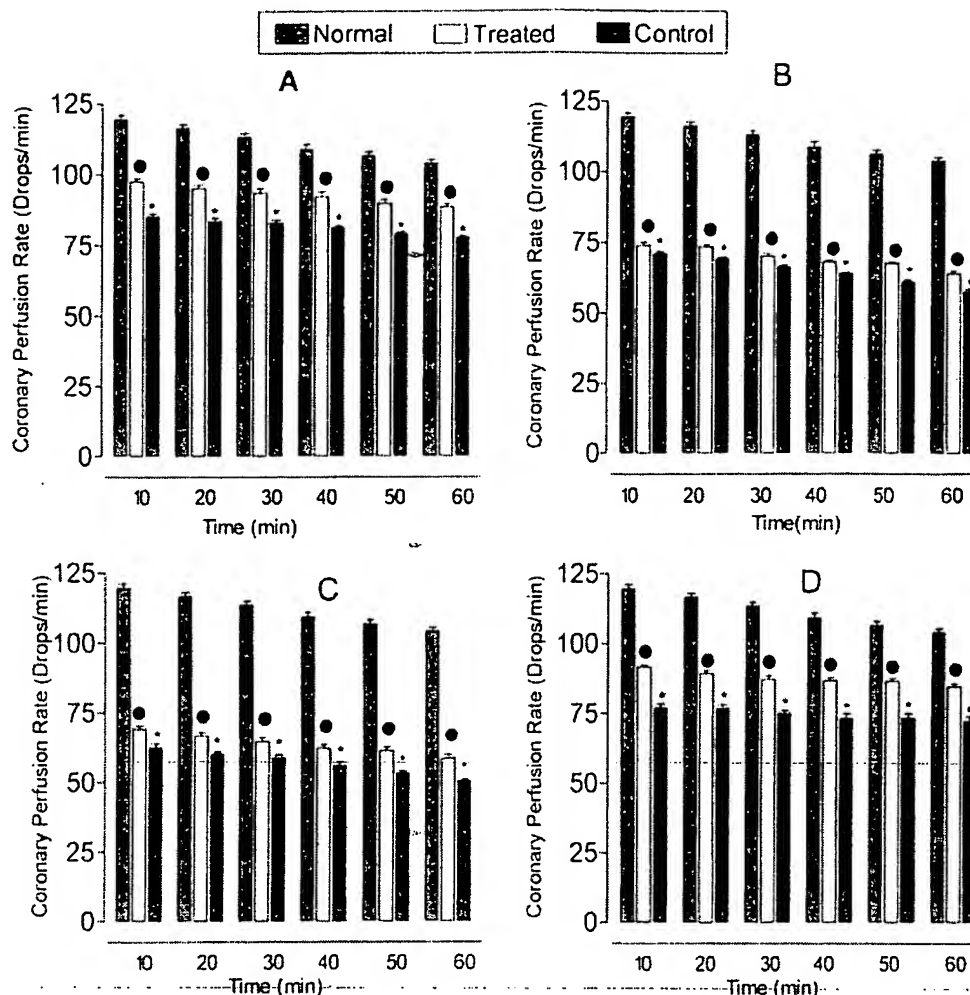


Fig. 4. Coronary perfusion rates of infarcted plus nimesulide treated rabbits vs. infarcted plus saline treated rabbits (controls) on day 2 (A), on day 4 (B), on day 8 (C) and on day 16 (D) after infarction. N=6, $p < 0.05$ for control rabbits compared to nimesulide treated group, $p < 0.05$ for nimesulide treated rabbits compared to normal, non-infarcted group. Rabbits in the infarcted plus nimesulide treated group showed significant improvement in the coronary perfusion rate as compared to the rabbits in the infarcted and saline treated group on each corresponding day after infarction.

this treatment continued up to the day of sacrifice. Similarly the other group was treated with nimesulide on the day of infarction and this treatment continued up to the day of sacrifice. Third group was non-infarcted, normal rabbits.

On day 2 post-infarction, CPR on the two groups of the rabbits were compared. Rabbits in the nimesulide treated group showed significant improvement in CPR ($p < 0.05$) as compared to the saline treated rabbits. On day 4 post-infarction, rabbits in the nimesulide treated infarcted group again displayed significant improvement in CPR ($p < 0.05$) as compared to the saline treated rabbits. It means that nimesulide treatment made recovery in CPR towards normal, although still very low then normal ($p < 0.05$). On day 8 of post-infarction, there was significant improvement in CPR of nimesulide treated infarcted rabbits ($p < 0.05$). On day 16 of post-infarction CPR of the two groups of infarcted rabbits were compared. Nimesulide

treated infarcted rabbits displayed significant improvement ($p < 0.05$) than the saline treated infarcted rabbits.

On day 16 of post-infarction, values of CPR of both groups of infarcted rabbits better than the infarcted rabbits of day 4 and day 8 post-infarction. On day 16 post-infarction rabbits treated with nimesulide showed maximum recovery. These values were very close to those of nimesulide treated rabbits at day 2 post-infarction. These values of CPR, however, were still significantly lower than the normal ($p < 0.05$), nevertheless, showing that on day 16 post-infarction, rabbits in the nimesulide treated group made significant recovery.

DISCUSSION

In the present study, we have developed a model for experimental MI. The main features of this model follow changes seen in humans after MI. For example, the

Table I. Coronary perfusion rates (CPR) of normal, infarcted plus saline, infarcted plus nimesulide treated rabbits on day 2, 4, 8 and 16 after infarction

Time (Min)	Coronary Perfusion Rate (Drops/Min)								
	Normal	Day 2		Day 4		Day 8		Day 16	
		Sal (Infarcted)	Nim (Infarcted)	Sal (Infarcted)	Nim (Infarcted)	Sal (Infarcted)	Nim (Infarcted)	Sal (Infarcted)	Nim (Infarcted)
10	117±6	85±7	98±7	71±6	74±5	74±5	76±5	75±4	86±3
20	114±7	84±6	95±5	69±5	73±4	73±5	76±6	74±3	84±4
30	112±7	83±7	93±5	66±6	70±5	70±4	75±7	73±5	83±3
40	107±8	81±8	92±7	64±4	68±4	68±3	73±6	72±4	83±4
50	105±9	79±6	90±4	61±4	67±4	67±5	73±6	72±4	82±4
60	102±7	78±5	88±8	57±5	64±3	64±6	72±7	70±3	80±4

changes seen in the levels of TPI and CPK from myocytes. These findings further corroborated the induction of MI by ISP. The application of this model for evaluating drugs which might interfere with clotting and heart attacks, in particular nimesulide, a COX-2 inhibitor which also known to reduce oxidative stress and exhibit antioxidant properties.

The other class in particular aspirin, non-steroidal inflammatory drugs (NSAIDs), which is known to inhibit platelet aggregation mediated by COX. Its has clinical efficacy in ischaemic heart disease (Saeed *et al.*, 2001). Its beneficial effects are probably due to its antithrombogenic actions as an inhibitor of platelet aggregation. However, a direct cardioprotective effect of aspirin on ischaemic myocardium has not been demonstrated. Studies have shown that aspirin did not affect myocardial infarct size after canine coronary artery infarction (Bonow *et al.*, 1981). It has been reported (Moberg *et al.*, 1998) that aspirin caused a 15-fold increase in guinea pig heart and concluded that nonspecific COX inhibition leads to myocardial oxygen deprivation. Thus, selective COX-2 inhibition seemed to have clear therapeutic advantage.

COX-2 is the isoform responsible for the enhanced production of prostaglandins that mediate inflammation and is the target enzyme for the anti-inflammatory activity of NSAIDs (Lecomte *et al.*, 1994). Induction of COX-2 in ischaemic myocardium is thought to increase the production of proinflammatory prostanoids and contribute significantly to the ischemic inflammation (Saito *et al.*, 2000). Furthermore, COX-2 expression is induced by proinflammatory mediators, particularly by cytokines and reactive oxygen species (Belton *et al.*, 2000), and its expression has been found in animal models of atherosclerosis as well as in human atherosclerotic tissues (Baker *et al.*, 1999; Schonbeck *et al.*, 1999). It has proposed that atherosclerosis is a process with inflammatory features (Koenig, 2001) and selective COX-2 inhibitors may potentially have antiatherogenic effects by the virtue of inhibiting inflam-

mation (Mukerjee *et al.*, 2002).

Improvement in the coronary perfusion rate found in the present studies (Fig. 4) strongly suggests that coronary vasodilatation occurs through endothelial dependant NO formation. An increasing body of evidence suggests that oxidative stress accounts in large parts for endothelial dysfunction (Cai *et al.*, 2000). There is evidence that COX-2 may be a source of oxygen radicals itself (O'Banion, 1999) and therefore, inhibition of this enzyme activity by nimesulide may reduce oxidative stress. The link between increased oxidative stress and reduced bioavailability of NO has been well established (Cai *et al.*, 2000). Furthermore, endothelial dysfunction in patients with coronary artery disease is beneficially reversed by anti-oxidative agents, such as vitamin C (Hetzer *et al.*, 1996). In fact selective COX-2 inhibition holds the potential to beneficially impact outcome in patients with cardiovascular disease (Chenevard *et al.*, 2003).

More recently, it has been demonstrated that selective COX-2 inhibition improves endothelial-dependent vasodilatation and reduces low-grade chronic inflammation and oxidative stress in coronary artery disease (Chenevard *et al.*, 2003).

ACKNOWLEDGEMENTS

We thank Mr. Ghulam Rasool for editorial assistance.

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Review

Current status of the therapeutic uses and actions of the preferential cyclo-oxygenase-2 NSAID, nimesulide

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Received: 11 November 2005; revised: 12 March 2006; accepted: 24 March 2006

Abstract. This review summarizes the principal therapeutic responses to the preferential COX-2 NSAID, nimesulide, in treating musculo-skeletal joint symptoms and various acute and chronic pain conditions and the mode of action in relation to therapy in these states.

In extensive studies in laboratory animal models and clinical trials in patients nimesulide has been found to have potent analgesic, anti-inflammatory and anti-pyretic activities. It is approved for use in over 50 countries worldwide (including those in the EU, South and Central America, China, India and some other South-East Asia) for the treatment of acute pain, the symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. Its mode of action in these states is related to the preferential inhibition of the production of cyclo-oxygenase-2 (COX-2) and other inflammatory mediators whose production is controlled by stimulation of cyclic-3',5'-adenosine monophosphate (cAMP); this means that nimesulide is a multi-factorial drug in controlling inflammation and pain.

The adverse reaction profile of nimesulide is, in general, like that of other NSAIDs. It does, however, have relatively low occurrence of gastro-intestinal (GI) side effects which is related to its low propensity to inhibit the physiologically important COX-1 in the GI mucosa and important physico-chemical properties (high pKa of 6.5 and lipophilicity) as well as inhibiting of mast cell derived histamine and acid secretion in the stomach. In contrast with the coxibs, nimesulide has not been found to have appreciable cardiovascular toxicity.

Key words: NSAID; Anti-inflammatory; Analgesic; Side-effects; Sulphonamide; Cyclooxygenase

Introduction

It is well-established that non-steroidal anti-inflammatory drugs (NSAIDs) have fundamental actions in controlling inflammation and in pain relief (Kean and Buchanan, 2005). They all inhibit the production of prostaglandins through the inhibition of COX-1 and COX-2, these being the enzymes responsible for their synthesis (Vane and Botting, 2001; Rainsford, 2004a). In addition, however studies in experimental and clinical models have clearly demonstrated other activities on pro-inflammatory mediators involved in the actions of NSAIDs in providing relief from inflammation and pain (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Celotti and Laufer, 2001; Tarnawski and Jones, 2003; Rainsford, 2004;). Among these mechanisms are the inhibition of leucocyte accumulation at inflamed sites, activation and expression of cell surface receptors, of angiogenesis, cell apoptosis, reactive oxygen species (ROS, or oxyradicals and nitric oxide) and their actions, and the regulation of non-prostanoid lipid mediators (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Tarnawski and Jones, 2003; Rainsford 2004a, 2004b; Celotti and Laufer, 2001; Serhan, 2004)

Aside from individual variations in pharmacological effects NSAIDs also differ substantially in the pharmacokinetic, pharmacological, pharmacodynamic and in their clinical profiles (Hart and Huskisson, 1984; Brogden, 1986; Bannwarth et al., 1989; Levy and Smith, 1989; Netter et al., 1993; Evans, 1996; Hayball, 1996; Rainsford, 1996; Lefkowitz 1999; Heyneman et al., 2000; Verbeeck 1990; Celotti and Laufer, 2001; Day 2001; Landoni and Scoraci, 2001; Bijlsma 2002; Tarnawski and Jones, 2003; Rainsford et al., 2005a, 2005b; Huntjens et al., 2005). Since they have essentially the same therapeutic properties in controlling pain, inflammation and fever, the scale of adverse effects often remains the main discriminator for choosing between individual NSAID (Hart and Huskisson, 1984; Rainsford, 1996; Kean and Buchanan, 2005).

Gastrointestinal (GI) adverse events remain the main concern in the use of NSAIDs and GI tolerability is a central issue for clinicians who prescribe these drugs (Rainsford, 1996, 2001; Rothstein, 1998). Other important side effects should also be taken into consideration when prescribing these drugs such as allergic reactions, skin adverse reaction, renal complications, alteration of hepatic enzyme levels and rarely hepatopathies (Rainsford, 1996, 1997, 2001; Rothstein, 1998; Teoh and Farrell, 2003; Uemura et al., 2003; Simon and Namazy, 2003; Sanchez-Borges et al., 2002, 2003; McGettigan et al., 2000).

Finally, the recent withdrawal of two of the newer COX-2 selective NSAIDs, rofecoxib and valdecoxib because of serious cardiovascular reactions (the latter also due to serious skin reactions), as well as the withdrawal or limitations on the use of celecoxib in some countries poses question about the cardiovascular (CV) safety profile of the whole NSAIDs class (Rainsford, 2005c; Khanna et al., 2005; Oster and Hazleman, 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). The FDA and EMEA took different positions on this issue. The FDA took the view that the issue concerning the CV risks of coxibs raised concerns about the CV safety of all NSAIDs (US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). In contrast, the EMA considered the CV risk of coxibs was clearly greater than that of other NSAIDs whether preferential or non-selective COX-2 inhibitors (which they grouped as non-selective COX-2 inhibitors) (European Medicines Agency, 2005a, 2005b).

Traditional NSAIDs and selective COX-2 inhibitors

In 1971, Professor Sir John Vane and colleagues postulated that aspirin and other NSAIDs, produced their anti-inflammatory and analgesic effects by inhibiting the biosynthesis of prostaglandins, through the blockade of the COX enzyme (Vane, 1971; Ferreira et al., 1971; Flower et al., 1972). In the early 1990's, it became evident that two isoforms of the COX enzyme were actually involved in the production of prostaglandins (Rainsford, 2004a, Vane and Botting, 1995, 2001). In particular, it was showed that the COX-1 isoform is responsible for the production of prostaglandins which contribute to maintain the homeostasis in key organs such as the stomach and kidney as well as influence mechanisms linked to the blood coagulation and vascular functions. The other isoform, COX-2, was found to be mainly induced by inflammatory and painful stimuli and to cause the formation of prostaglandins which play a key role in the inflammation and neural responses, although more recent research attributes a role in the maintenance of homeostasis to this isoform as well (Vane and Botting, 1995, 2001; Rainsford, 2004a).

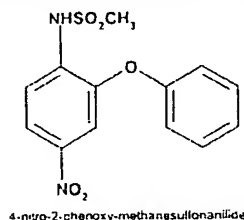
Non-selective NSAIDs inhibit both COX-1 and COX-2 by binding reversibly or irreversibly to the enzyme (Vane and Botting, 1995; Rainsford, 2004a). The toxic effects of these non-selective NSAIDs in the gastro-intestinal tract,

kidney and vascular systems are considered, in part, to be due to inhibition of the synthesis of physiologically important ("housekeeping") prostaglandins (PGs) E_2 and I_2 in these systems (Vane and Botting, 1995, 2001; Rainsford, 2004a). Inhibition of COX-2 selectively inhibits the synthesis of PGE_2 and other PGs involved in inflammation and mediating neural signals in pain pathways Vane and Botting, 1995, 2001; Rainsford 2004a, 2004b; Rainsford et al., 2005). NSAIDs exhibit different degrees of selectivity in their ability to differentially block COX-1 or COX-2 (Vane and Botting, 1995, 2001; Rainsford, 2004a; Tarnawski and Jones, 2003). While there are many other factors that are involved in the development of adverse reactions (e.g. in the GI tract and kidney) the involvement of COX-1 inhibition plays a significant part (Rainsford, 1996, 2001; Hotz-Behofsits et al., 2003; Tarnawski and Jones, 2003).

In late '90s based on the assumption that the inhibition of COX-1 is the main cause of GI bleeding, a new class of highly selective COX-2 inhibitors, the so-called coxibs, were developed (de Laval et al., 2000; Vane and Botting, 2001; Rainsford, 2004a). Their purpose was to inhibit, at recommended therapeutic doses, mainly COX-2, with little if any effects on COX-1 (Vane and Botting, 2001; Rainsford, 2004a). The coxibs were, therefore, looked at as a safer alternative to traditional NSAIDs, especially their GI safety profile. Evidence from short-term studies showed that the coxibs had lower gastro-ulcerogenic effects in animals and humans (Feldman and McMahon, 2000). Since their discovery certain physicochemical properties (high pKa, lipophilicity) have been identified that may also account for their low acute GI ulcerogenicity (Rainsford, 1999a). In long-term studies in patients with arthritic conditions this was less marked and the incidence of serious GI events from coxibs proved similar to that from NSAIDs (Bjarnason and Rainsford, 2001a, 2001b; Schoenfeld, 2001; Jüni et al., 2002).

The inhibitory activity of NSAIDs towards the two COX isoforms is only one of the aspects which play a role in their analgesic and anti-inflammatory activity. Aside from the degree of selectivity toward COX isoforms, NSAIDs can be distinguished according to other characteristics such as their chemical structure, as well as their acidic and non-acidic chemical characteristics (e.g. pKa) (Rainsford, 1999a, 2004c). Their biological activities are also due to their relative effects on the production of inflammatory and pain mediators which account for their anti-inflammatory, analgesic activities (i.e. central or peripheral) antipyretic and other pharmacological properties. Physico-chemical factors are well-known to influence pharmacokinetics of NSAIDs (Graf et al., 1975; Brune et al., 1977; Netter et al., 1993) and especially the rate of GI absorption and uptake into inflamed cells or synovial tissues and cerebrospinal fluids (Netter et al., 1993; Rainsford, 1999a, 2004c; Shimizu et al., 2003; Pehourcq et al., 2004;). NSAIDs with low pKa values (e.g. carboxylic acids) have a greater tendency to be irritant to the gastric mucosa as a consequence of their selective absorption into GI mucosal cells (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Hotz-Behofsits et al., 2003; Rainsford, 1999a; Sigthorsson et al., 2000a, 2000b) leading to ion trapping (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Sigthorsson et al., 2000), as well as uptake into mitochondria and

Physicochemical properties of nimesulide



- Non-acidic NSAID, pKa 6.4
 - $\approx 100\%$ unionized at acidic pH in gastric environment
 - Low water solubility: 5.5mg/L (25°C)
 - MW 308.3 Da
 - Log P (Octanol/Water, pH 7.4) = 1.8
 - Hydrogen bond donors: 1
 - Hydrogen bond acceptors: 6
- } with pKa results in high GI permeability, but low gastric irritancy

Fig. 1. Physico-chemical properties of nimesulide.
From Dr Alberto Bernareggi and reproduced with his permission.

uncoupling of oxidative phosphorylation (Sigthorsson et al., 2000) leading to reduction in ATP production and apoptosis (Redlak et al., 2005). These physicochemical features of NSAIDs also underlie their renal effects (Brune et al., 1977). Drugs with relatively higher pKa than the carboxylates such as nimesulide (pKa 6.5) (Fig. 1) while being well absorbed probably have a lower propensity to lead to ion trapping in mucosal cells (Rainsford, 1999a; Sigthorsson et al., 2000) and consequently are less irritant to the mucosal cells (see later section on Adverse Reactions and Relative Safety).

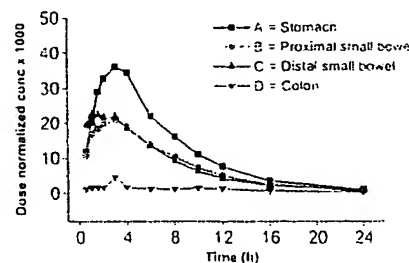
The Development of Nimesulide

Nimesulide was developed by Dr. George Moore and colleagues at Riker Laboratories (later acquired by 3M Co.) (Rainsford, 2005a). The discovery of nimesulide preceded the discovery of cyclo-oxygenase and the key roles of prostaglandins in inflammation and pain. The rationale for the design was actually based on the premise that free radicals were critical factors in chronic inflammation disease and scavenging of these radicals might have novel anti-inflammatory activities in the control of chronic inflammatory conditions (Swingle et al., 1985; Rainsford, 2005a).

Following initial unsuccessful observations on fluoroalkane-sulfonamides they modified their strategy to incorporate a 4-nitro- group into the sulphonamide structure to achieve oxyradical scavenging and this led to the synthesis of 4-nitro-2-phenoxy-trifluoromethane-sulfonamide. The designated compound, R-805, was found to have the best therapeutic ratio compared with reference NSAIDs available at that time (Rainsford, 2005a). The chemical name of the compound, 4-nitro-2-phenoxy-methane-sulphonamide served as the basis for the generic name of the drug, i.e. nimesulide. Subsequently in 1980 nimesulide was licensed by Helsinn Healthcare SA (Switzerland) who proceeded to invest in extensive investigations on the drug. These gave a basis for comprehensive investigations that allowed for the worldwide registration and commercialisation of the drug. These studies also led to identification of the multi-factorial basis for the actions of nimesulide.

Regional absorption from GI tract

Nimesulide absorption occurs mainly in the upper part of the GI tract.



A (control leg): 100mg nimesulide dissolved in PEG-400 and given in gelatine capsules. B, C, D: 100mg nimesulide given in IntelliSite® capsule, with drug release in the proximal (B) and distal small bowel (C), and in the ascending colon (D).

Pharmaceutical Profiles 1999

Fig. 2. Plasma concentrations of nimesulide normalized to dose following selective introduction into different regions of the gastro-intestinal tract. These data show that about 70% of the dose of the drug taken orally is absorbed in the stomach, while about 12% is absorbed in the small bowel and virtually no absorption occurs in the colon.

Nimesulide was first licensed and marketed in Italy in 1985, over 20 years ago. Subsequently, it has become the most prescribed and used NSAID in that country. It is now marketed in over 50 countries world-wide and in some is amongst, if not, a market leader.

Mode of Action of Nimesulide

There have been several reviews published over the years on the pharmacological properties of nimesulide (Ward and Brogden, 1988; Davis and Brogden, 1994; Famaey, 1997; Anonymous, 1998; Bennett and Villa, 2000; Bennett, 2001). More recently, a monograph has been published on nimesulide which includes all the main pharmacokinetic, pharmacological, clinical and chemical properties of this drug (Rainsford, 2005b).

Pharmacokinetics

Key features of the pharmacokinetics of nimesulide, which are important in relation to its pharmacological actions, include:

- Rapid and complete absorption from the upper gastrointestinal tract (Fig. 2); peak plasma concentrations ranging from 3.0-5.0 mg/L being reached at 1-3 h after oral ingestion of the recommended daily dose of 100 mg b.i.d. (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Tissue distribution in rats (Fig. 3) shows rapid accumulation in fat, liver, kidney, with some uptake into brain tissue. In rats, high fractional binding of the drug and its principal 4-hydroxy-metabolite to plasma proteins, principally albumin, ensures moderately low volume of distribution with $V_d/F \approx 0.2$ to 0.4 L/Kg (Bernareggi, 1998; Bernareggi and Rainsford, 2005a). Clearance is rapid such that most of the drug is eliminated in rats and humans by 24 h (Bernareggi, 1998; Bernareggi and Rainsford, 2005).

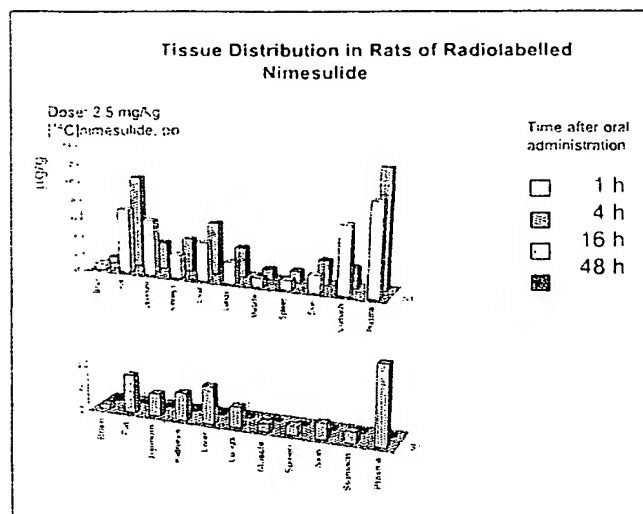


Fig. 3. Distribution in major organs of radioactive labelled-nimesulide in rats following oral administration of 2.5 mg/kg of the drug.

The upper bar graph shows the concentration ($\mu\text{g/g}$ wet weight) of nimesulide and its principle 4-hydroxy-metabolite at 1 h (front bars) and 4 h (at rear), while the bottom graph shows the concentration of these at 16 h (front bars) and 24 h (at rear) respectively.

There is widespread distribution of radioactively labelled drug within 1 h of oral administration with relatively high concentrations being present in the plasma, fat, stomach, jejunum, liver, kidneys and lungs. The presence in fat reflects the relatively high liposolubility of the drug. Although there is some uptake into the brain at 1–16 h this is not at a high level compared with the plasma concentration of the drug. The combined-tissue to plasma ratio is <1 and there is no accumulation of the drug in major organs. In humans the ratios of tissue/plasma drug concentrations in synovial and peripheral tissues are similar to those in rats.

There is no significant difference in the pharmacokinetics of nimesulide between rats and humans. The plasma half-life of nimesulide in humans is approximately 10 h, which is similar to that in rats (12 h).

- There is similar bioequivalence from different oral dosage forms (tablets, granules, suspension) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Food has a modest effect on total bioavailability; a relatively high fat American breakfast reducing peak plasma concentrations (C_{max}) by about 20% but there is no effect on the T_{max} or total bioavailability ($AUC_{0-15\text{h}}$) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Liver metabolism is principally due to (a) oxidation to form hydroxylated metabolites via cytochrome P_{450} 2C9, 2C19 and possibly CYP1A2, with subsequent glucuronidation and sulphation of the phenolic hydroxyl groups, and (b) reduction of the nitro-group to an amine (Bernareggi, 1998; Bernareggi and Rainsford, 2005). Nitroso- and hydroxylamine intermediates most likely occur in the reduction of the nitro-group (Bernareggi and Rainsford, 2005).

While nimesulide produces a considerable number of metabolites, the principal metabolite is the 4-hydroxy-derivative which, though generally less potent, has similar pharmacological actions to that of the parent drug (Rainsford et

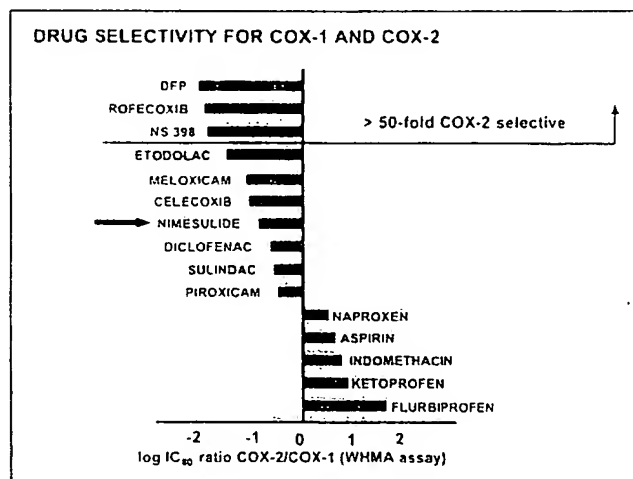


Fig. 4. *In vitro* selectivity of NSAIDs for COX-2 compared with COX-1. Based on data from Warner et al. (1999). Here there IC_{50} molar values for the inhibition of these two enzymes are compared as this is considered to give a closer representation of the likely effects in relation to the plasma concentrations of the drugs in humans.

COX-2 and anti-inflammatory activity

A large number of experimental investigations in animal models (Rainsford et al., 2005) and humans with arthritic and various pain states (Bianchi et al., 2005) have shown that nimesulide has anti-inflammatory activity which is comparable on a dose for weight basis with that of conventional NSAIDs such as diclofenac and indomethacin and the COX-2 selective drug, rofecoxib.

The effects of nimesulide, like that of other NSAIDs on COX-2 are among the mechanisms involved in the anti-inflammatory actions of this drug. The preferential COX-2 selectivity of nimesulide is a central feature of the anti-inflammatory as well as analgesic effects of this drug (Rainsford et al., 2005). Demonstration of this effect has been shown in a conventional *in vitro* and *ex vivo* assays. Among the *in vitro* assays used to define COX-1 and COX-2 selectivity of NSAIDs that developed by Warner and co-workers (Warner et al., 1999), known as the William Harvey (Institute) Modified Assay (WHMA) in whole human blood (Fig. 4) has become generally accepted to most closely represent that known to occur *in vivo* and best characterized in relation to the plasma pharmacokinetics of the drugs. The ratio of COX-2/COX-1 (which is a measure of COX-2 selectivity) in the WHMA data was found to range between diclofenac and etodolac and was close to that of celecoxib (Fig. 4). Yet the COX-2/COX-1 ratio of nimesulide is clearly out of the range of rofecoxib and NS-398, both of which are highly selective inhibitors.

To establish the significance of COX-2 selectivity in relation to GI effects and platelet function *ex vivo* studies were performed in human volunteers who had ingested either 100 mg nimesulide b.i.d. or naproxen 500 mg b.i.d. for 14 days and the COX-1/COX-2 effects were determined in blood and GI mucosa. There was no COX-1 – dependent platelet aggregation produced by nimesulide and it only

(TxA₂) and gastric mucosal production of PGE₂ and 6-keto PGF_{1α} in endoscopic biopsies (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000a, 2000b; Shah et al., 2001). Whole blood stimulated *ex vivo* with *Escherichia coli* lipopolysaccharide (LPS) from the nimesulide-treated subjects produced 91–93% inhibition of PGE₂ compared with control values after 3–10 days treatment.

In comparison, the ingestion of naproxen 500mg b.i.d. for 14 days caused significant reduction in serum TxB₂ production (by 98% of initial control values), gastric mucosal PG production by 76–82%, and blocked COX-1 dependent platelet aggregation. The LPS-stimulated whole blood PGE₂ production was significantly reduced by 74–77% of control values over 3–10 days *ex vivo*; the latter being less than that observed with nimesulide (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001).

The significance of these observations on COX-2 preferential effects of nimesulide on the gastro-intestinal (GI) effects of the drug were shown in upper GI endoscopic observations performed in the same volunteers and parallel studies of intestinal permeability using specific biomarkers. In both studies nimesulide had little or no effects on the Lanza scores of gastro-duodenal mucosa or intestinal permeability whereas naproxen produced significant gastric injury (44% of subjects showing >10 erosions or haemorrhagic areas) and increased intestinal permeability. Furthermore, naproxen caused a significant two-fold increase in excretion of faecal calprotectin (a marker of intestinal inflammation) above baseline whereas nimesulide was without significant effects on the excretion of this biomarker (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001).

These results represented the first conclusive evidence of COX-2 selectivity of an NSAID being paralleled in humans by lack of significant effects on GI mucosal integrity. These observations are supported by a large amount of studies in laboratory animal models (Sigthorsson et al., 2000) (reviewed – see Bjarnason et al., 2005; Rainsford et al., 2005) showing little or no effects of nimesulide on GI mucosal production of prostaglandins coincident with low GI mucosal injury from this drug.

Several actions of nimesulide may also account for the low GI ulcerogenicity of the drug aside from sparing of COX-1 activity in the mucosa and physico-chemical properties of the drug that limit its accumulation in mucosal cells (Bjarnason et al., 2005). Among these actions are the effects on mast cell degranulation and release of histamine, and inhibition of histamine stimulated acid production which maybe a consequence of elevation of cyclic 3',5'-AMP by nimesulide (Bjarnason et al., 2005) (see later). The lack of stress-synergy in expression of irritant actions of the drug on the gastric mucosa, such as seen with other NSAIDs may also be a factor of significance in the low ulcerogenicity of nimesulide (Rainsford, 1975, 1977).

The pharmacological profile of nimesulide with particular reference to its inhibitory activity on the COX enzymes, has been evaluated in various *in vitro* models. Although results vary depending on study conditions, nimesulide showed a higher affinity for the COX-2 enzyme (Rainsford et al., 2005). This is also supported by molecular modelling studies which showed that blockade of COX-2 is due to the

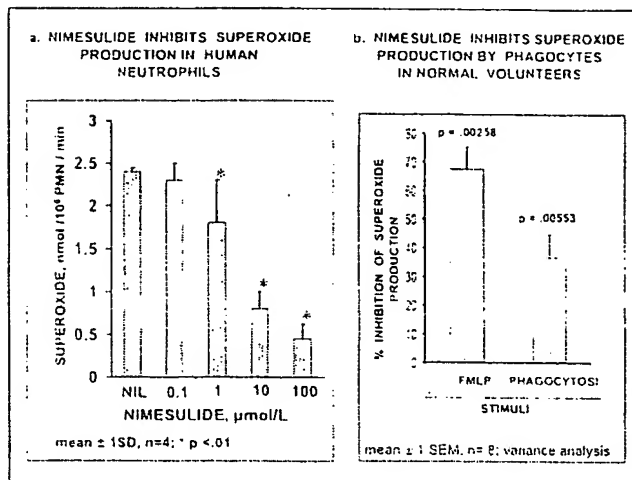


Fig. 5. Actions of nimesulide on neutrophil reactive oxygen species (ROS). Effects of nimesulide on superoxide production by human neutrophils *in vitro* (a) and on superoxide and phagocytosis by neutrophils *ex vivo* following ingestion by human volunteers of 100mg nimesulide (b).

a. Based on data from Bevilacqua et al. (1994)

b. Based on data from Ottonello et al. (1992)

interaction of nimesulide with the larger channel in COX-2 compared with COX-1 (Rainsford et al., 2005). In these experimental models nimesulide was also found to have some weak inhibitory activity on the COX-1 isoform (Rainsford et al., 2005), which might have therapeutic advantages in relation to prevention of thrombosis in patients with atherosclerosis.

Nimesulide, like some classical NSAIDs exhibits a considerable degree of anti-inflammatory activity as a consequence of various inhibitory effects on polymorphonuclear neutrophil leucocytes (PMNs) (Dallegrì et al., 1990, 1992a, 1992b, 1995; Ottonello et al., 1992, 1993, 1995, 1999; Capecchi et al., 1993; Verhoeven et al., 1993; Bevilacqua et al., 1994; Dapino et al., 1994; Tool and Verhoeven, 1995; Bennett and Villa, 2000; Bennett, 2001; Mouithys-Mickalad et al., 2000; Nakatani et al., 2001; Gomez-Gaviro et al., 2002; Bravo-Cuellar et al., 2003; Kimura et al., 2003; Rainsford et al., 2005). These effects are, in some cases, relatively potent compared with the activities of other NSAIDs, and occur within the drug concentrations in plasma or synovial fluids encountered during therapy with the drug (Rainsford et al., 2005; Bennett and Villa, 2000; Bennett, 2001). Thus, nimesulide inhibits chemotaxis and superoxide production at $\geq 1 \mu\text{mol/L}$ (Fig. 5) and production of platelet activating factor, leukotriene B₄ and hypochlorous acid (HOCl) from PMNs at $\geq 10 \mu\text{mol/L}$ in concentrated-related manner (Dallegrì et al., 1990, 1992a, 1995; Ottonello et al., 1992, 1993, 1995; Verhoeven et al., 1993; Bennett and Villa, 2000; Bennett, 2001). At $\geq 5 \mu\text{mol/L}$ nimesulide inhibits release of elastase and other markers of neutrophil degranulation that contribute to cartilage destruction in osteoarthritis (OA) and related conditions (Ottonello et al., 1993; Nakatani et al., 2001). At higher "supra-therapeutic" concentrations ($\geq 20 \mu\text{mol/L}$) nimesulide inhibits neutrophil adherence to endothelial cells, shedding of L-selectin and transendothelial migration (Fig. 6) (Dapino et al., 1994; Gomez-Gaviro et al., 2002).

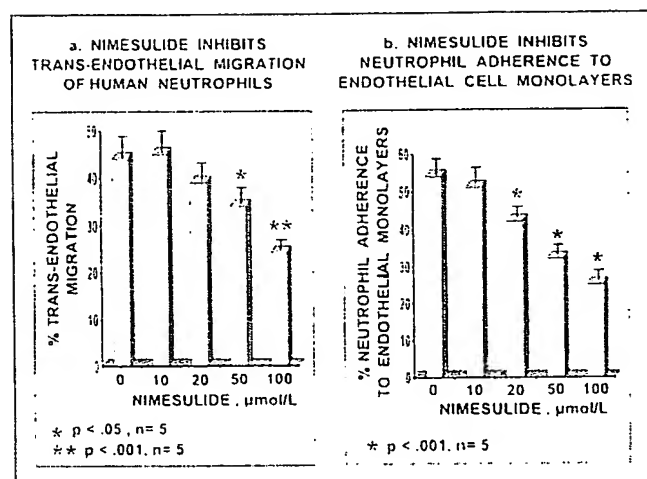


Fig. 6. Actions of nimesulide on neutrophil-endothelial cell interactions. Effects of nimesulide on the migration of neutrophils through endothelial cells (a) and on neutrophil adherence to endothelial cell monolayers (b).

a, b. Based on data from Dapino et al. (1994)

Confirmation of the actions *in vivo* in humans of nimesulide on neutrophil oxidative reactions has been provided by Ottonello and co-workers (1992) who showed that oral ingestion of 100 mg nimesulide lowered the phagocytic superoxide generation of neutrophils in response to opsonized zymosan particles and *N*-formylmethionyl-leucyl-phenylalanine (Fig. 5).

In contrast to the effects on neutrophils, nimesulide ($>0.1 \mu\text{mol/L}$) reduces the survival of human monocytes suggesting that this drug may have selective actions on apoptosis or other actions that affect growth of monocytes (Sawada et al., 2000).

An important action of nimesulide not observed with many other NSAIDs is its ability to inhibit the release of histamine from mast cells (Casolaro et al., 1993; de Paulis et al., 1997; Kolaczowska et al., 2002). This effect probably has significance not only in vasodilatation in acute inflammation but also for the wide range of actions of histamine now known to be of importance in chondrocytes and other cells involved in joint manifestations of arthritic diseases (Tanaka et al., 1997).

In addition to effects on mast cells, nimesulide inhibits chemotaxis and production of reactive oxygen species (ROS) and leukotriene C_4 production by eosinophils (Tool et al., 1996); these effects may be of significance in control by the drug in airways inflammation and allergic reactions although proof of the clinical effects is not yet available.

It has been postulated that a central or basic action of nimesulide in elevating intracellular levels of the key cell signal, cyclic 3',5'-AMP (cAMP) may account for the wide-ranging inhibitory effects on inflammatory cells and release of cartilage degrading enzymes (e.g. matrix metalloproteinases) (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004). Figure 7 shows the central role that elevation of cAMP plays in mediating these actions. Confirmation of the effect of nimesulide on cAMP in PMNs has been shown in which the activity of the enzyme that degrades cAMP, phosphodiesterase IV, is inhibited at concentrations

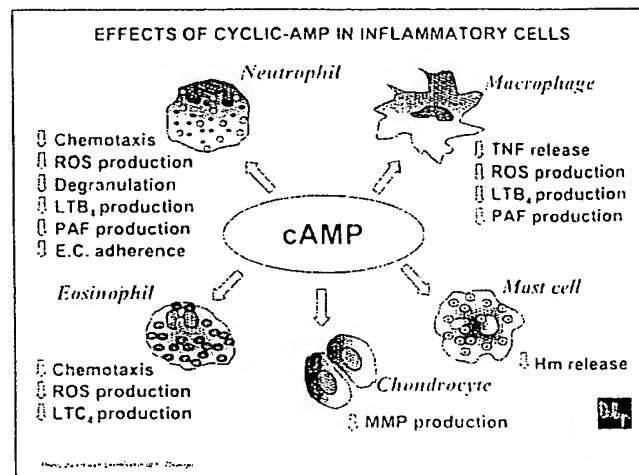


Fig. 7. The central actions on leucocytes, mast cells and chondrocytes of nimesulide as a consequence of regulation of cyclic 3',5'-adenosine monophosphate (cAMP). It is postulated that as nimesulide increases production of cAMP as a consequence of inhibition of phosphodiesterase-IV: this increased cAMP leads to reduced production of a wide range of inflammatory mediators by neutrophils, macrophages, mast cells and eosinophils. The reduction via cAMP in the cytokine stimulated release as well and the direct effects on the activity of metalloproteinases (MMP) especially of stromelysin (MMP-3), MMP-1 and MMP-8 from chondrocytes (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), may, with the actions of nimesulide in activating glucocorticoid receptors, may contribute to reduced degradation of cartilage in osteoarthritis.

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$\geq 1 \mu\text{mol/L}$ coincident with increase in intracellular cAMP. This increase causes activation of protein kinase A which leads to inhibition of the various functional responses shown in Figure 7.

The potential protective effects of nimesulide on cartilage-degradation may be due to inhibition of the activity and production of metalloproteinases (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), urokinase (Pelletier et al., 1997), expression of pro-inflammatory cytokines (Pelletier et al., 1997; Fahmi et al., 2001), increased production of plasminogen activator inhibitor-1 (Pelletier et al., 1997) as well as the induction and activity of COX-2 (Di Battista et al., 2001; Fahmi et al., 2001). Nimesulide reverses the inhibitory effects of interleukin-1 on cartilage proteoglycan synthesis, as well as inhibiting interleukin-1 induced production of oxyradicals by cartilage and nitric oxide by chondrocytes (Rainsford et al., 2002). Overall, the results from these various biochemical studies suggest that nimesulide might have a role in the protection of cartilage degradation in arthritic disease (Barracchini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), in contrast with other NSAIDs some of which may accelerate this degradation process (Rainsford et al., 1992; Walker and Rainsford, 1997). The therapeutic significance of these observations can be seen in clinical studies in which therapeutic doses of nimesulide, but not ibuprofen, showed to significantly decrease the serum levels of MMP's (Fig. 8), including stromelysin (or matrix metalloproteinase-3, MMP-3) (Kullick et al., 2002; Kalajdzic et al., 2002; Bevilacqua et al., 2004), which may be related to

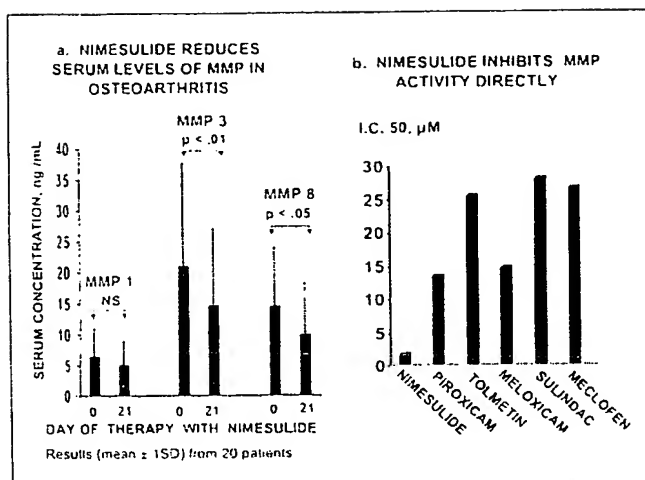


Fig. 8. Actions of nimesulide in reducing levels of metallo-proteinases (MMP's) in the serum of patients with osteoarthritis that had taken nimesulide [a], and of MMP enzymatic activity *in vitro* [b].

a. Based on data from Kullick et al. (2002)

b. Based on data from Barracchini et al. (1998)

reduction in the serum levels of hyaluronan (Bevilacqua et al., 2004), and the C-terminal cross-linking telopeptide of collagen II (Kalajdzic et al., 2002) both biomarkers which predicts a poor outcome of the osteoarthritis joint disease.

A recent observation by the Pelletier group concerning the effect of nimesulide in activating the glucocorticoid receptor and so producing inhibition of the transcription of COX-2 (DiBattista et al., 2001; Fahmi et al., 2001), so inhibiting the translation of the mRNAs for MMP's and pro-inflammatory cytokines (Pelletier et al., 1999). This may represent a novel and far-reaching action of the drug not seen with other NSAIDs. Further studies are, however, needed to confirm the effects of nimesulide on glucocorticoid receptor activation coincident with reduction in expression of the mRNA for proteins regulating production of the abovementioned inflammatory mediators.

In conclusion, nimesulide has a range of multi-factorial actions *in vitro*, some of which have been demonstrated *ex vivo* or *in vivo* in patients (Bennett and Villa, 2000; Bennett, 2001); these effects are summarised in Figure 9. Many of these are most likely related to core effects in causing inhibition of the production and actions of COX-2, cyclic AMP and glucocorticoid receptors, which appear to underlie the anti-inflammatory activity of nimesulide. The preferential inhibitory effects on COX-2, *ex vivo* inhibition of phagocytosis (as an effect related to ROS) and levels of serum MMP-3 and MMP-8 are actions of the drug that have been shown in humans. In models of inflammation in rats, nimesulide has been found to reduce PGE₂, TNF α and neutrophil accumulation in inflammatory exudates thus providing further support for the multi-factorial actions *in vivo*. These multiple actions of the drug mean that the expression of anti-inflammatory activity is a consequence of regulation of the production and actions of a wide range of mediators of inflammation in contrast to the sole dependence of effects on production of prostaglandins from COX-2 activity as observed with NSAIDs such as the coxibs.

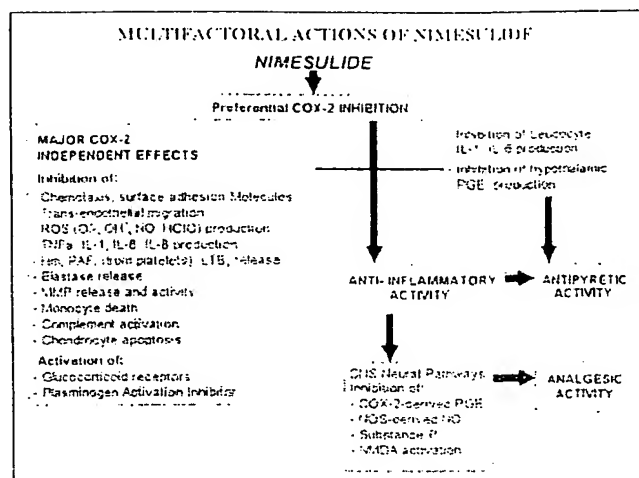


Fig. 9. Summary of the multi-factorial actions of nimesulide involving prostaglandin-related, and non-prostaglandin-related effects.

Abbreviations: COX-2, cyclo-oxygenase-2, TNF α , tumour necrosis factor- α , Hm, histamine, PAF, platelet activating factor, ROS, reactive oxygen species, MMP, metalloproteinase(s)

Analgesic Activity

The analgesic activity of nimesulide is partly due to the capability of reducing the activity of the CNS nociceptive system with an onset of action consistent with the pharmacokinetic characteristics of the drug (Rainsford et al., 2005). The well-established increase in prostaglandins in the central nervous system (CNS) during pain transmission is due to induction and activity of COX-2 (Yamamoto and Nozaki-Taguchi, 1996; Ohtori et al., 2004; Veiga et al., 2004; Hofacker et al., 2005), although there is some evidence that COX-1 may also be involved (Zhu et al., 2003). Furthermore, nitric oxide (NO) plays a significant role in mediating sensitisation in the transmission of pain in the CNS (Schulte et al., 2003; Schmidtke et al., 2003; Tassorelli et al., 2004). Its presence and sustained elevation is critical in maintaining central sensitisation whilst the inhibition of NOS as well as COX-2 reduces central sensitisation in pain models. Experimental studies in animal models have demonstrated that nimesulide inhibits COX-2 and nitric oxide synthases (NOS) in the spinal cord (Tassorelli et al., 2003) confirming the central action of the drug in humans (Sandrini et al., 2001, 2002).

Figure 10 shows the possible modes of action of nimesulide at the level of the dorsal horn which may represent a key region of the central nervous system affected by the drug. That central actions of nimesulide are important in control of spinal neurotransmission in humans is illustrated from the study shown in Figure 11 (Sandrini et al., 2001).

Some of the mechanisms of the analgesic actions of nimesulide that have been shown in experimental models require more extensive investigations in humans to establish the clinical significance of these actions. However, as nimesulide affects a considerable number of mediators involved in both peripheral and central nervous system mediation of pain relief in hyperalgesia (Rainsford et al., 2005).

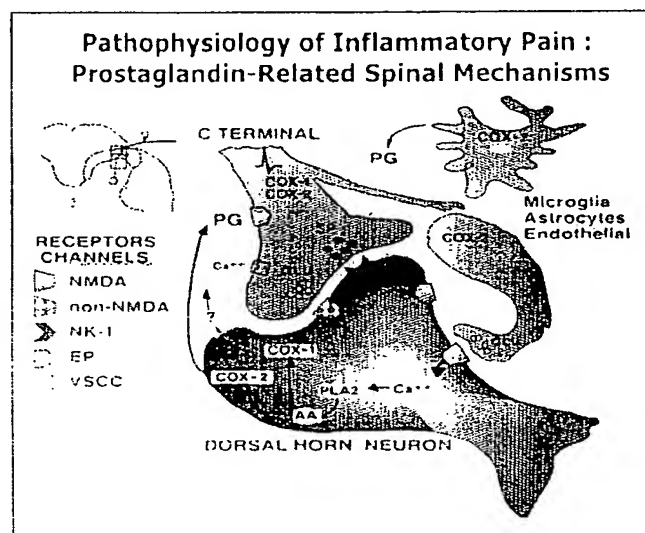


Fig. 10. Pathways involving prostaglandins (principally PGE₂) derived from cyclo-oxygenases 1 and 2 and their actions in mediating hyperalgesic responses to inflammatory pain in the dorsal horn. Induction of COX-2 during painful stimuli amplifies the production of PGE₂ and with this the stimulation of nerves impinging on and mediated from the dorsal horn via afferent nerves in the spinothalamic tracts of the central nervous system. PGE₂ production from activation of dorsal horn neurones by afferent inputs from C- and Aδ-fibres causes (a) release of glutamate which acts on NMDA and non-NMDA receptors, and (b) release of substance P which acts on neurokinin-1 receptors (NK-1). The activation of these receptors leads to increased flux of Ca²⁺ ions that activate phospholipase-A₂ which in turn hydrolyzes phospholipids and release of arachidonic acid which serves as a substrate for COX-1 and COX-2. Nitric oxide synthase of the neuronal type, nNOS, is also activated and the nitric oxide produced during neural stimulation contributes to the activation of afferent pathways.

Nimesulide inhibits release of PGE₂ and NO and so modulates neural transmission at the level of the dorsal horn. Whether sufficient concentration of the drug reach the dorsal horn to block COX-1 is not known. PGE₂ production from accessory cells (e.g. microglia, astrocytes) and endothelial cells also contributes to the cycle of activation of dorsal horn cells. From Bianchi et al. (2005); unpublished figure.

The fast onset of pain relief which is evident 15 min after oral intake of the drug is evident from studies in human volunteers where the spinal nociceptive transmission was determined after intake of nimesulide compared with placebo (Fig. 11) (Sandrini et al., 2001, 2002). These observations are paralleled in humans by the reduction of pain from ingestion of nimesulide which was apparent after 15 min from the administration, with a statistically significant superior onset of action being apparent versus the comparator drugs (Fig. 12) (Bianchi and Broggin, 2002).

In addition to affecting production of spinal PGE₂, nimesulide appears to influence the actions of NO in neural transmission (Sandrini et al., 2002). Undoubtedly, the rapid onset of analgesia by nimesulide is linked to the pharmacokinetic properties of the drug. Thus, after oral administration of 50 to 200 mg nimesulide tablets to healthy volunteers, plasma C_{max} values, ranging from 2.0 to 9.9 mg/L, are achieved quite rapidly within 1.7 to 3.2 h (Bernareggi, 1998). Studies in rheumatic patients have shown that relatively high nimesulide concentrations are present in inflamed synovial tissues and at earlier times than plasma

NIMESULIDE INHIBITS SPINAL NOCICEPTIVE TRANSMISSION

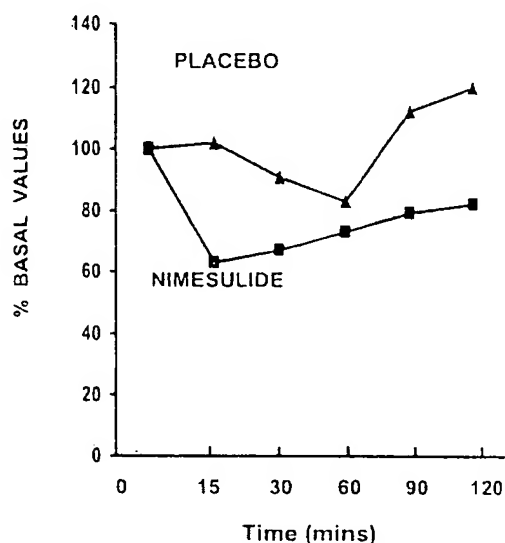


Fig. 11. Effects of nimesulide compared with placebo on spinal nociceptive transmission in human volunteers. From Sandrini et al. (2001).

PID (Pain Intensity Difference) Changes Following Treatment with Nimesulide, Mefenamic Acid and Placebo

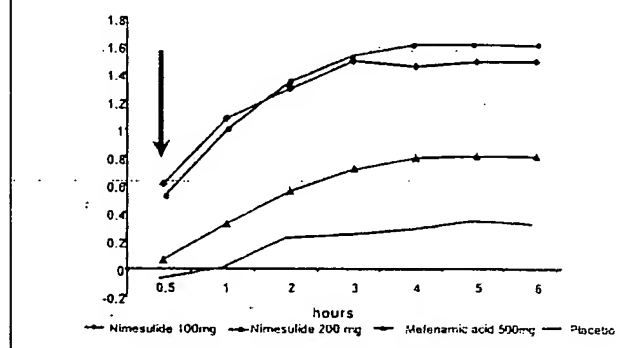


Fig. 12. Pain Intensity Difference (PID) Scores following dental surgery over a 6 h period following oral ingestion of 100 or 200 mg nimesulide compared with a comparable analgesic/anti-inflammatory dose of mefenamic acid and showing superior effects of both these NSAIDs over placebo.

The dental surgery pain model is one of the frequently used human pain models which are very responsive to NSAIDs and analgesics. The effects of NSAIDs have been found to relate to inhibition of PGE₂, substance P and other mediators of acute inflammation. From Ragot et al. (1994).

peak times (Ligniere et al., 1990). The rapid accumulation in synovial fluids is also accompanied by rapid reduction in synovial fluid concentrations of PGE₂ (Duffy et al., 2003), thus indicating the synovial fluid pharmacodynamics of nimesulide coincides with the expression of pharmacological actions of the drug.

There is, however, evidence of reduced bio-equivalence of some copy and generic versions of nimesulide that can affect the pharmacokinetics of the drug compared with that of the original formulation of nimesulide (e.g. Aulin®) (Maroni and Gazzaniga, 2005). Any reduction in bioavailability of nimesulide would be expected to result in lower efficacy. A gel formulation of nimesulide has been found to have pharmacokinetic properties like that of diclofenac gel with comparable absorptive properties that favour local application to inflamed tissues and joints (Sengupta et al., 1998; Bianchi et al., 2005).

Clinical Applications

Over 200 clinical trials have been conducted in more than 90,000 patients with nimesulide in a variety of acute and chronic inflammatory and painful conditions (Ward and Brogden, 1988; Rabasseda, 1996; Anonymous, 1998; Bianchi et al., 2005).

1. Acute pain

The rapid onset of action of nimesulide is particularly evident in a variety of painful conditions where acute inflammation is the most predominant component. Thus, nimesulide has been shown to consistently reduce pain and where studied the inflammatory reactions and found to be superior to placebo and comparable or in some cases better than reference NSAIDs in (a) the treatment of soft tissue injuries and extra-articular trauma (where the gel formulation also gives good pain relief) (Ward and Brogden, 1988; Calligaris et al., 1993; Dreiser and Riebenfeld 1993a, 1993b; Lecomte et al., 1994; Jenoure et al., 1998; Dhaon et al., 1998, 2000), (b) various ear, nose and throat (ENT) inflammatory conditions (e.g. otitis, sore throat) (Milvio, 1984; Bianchini et al., 1993; Ottavani et al., 1993), (c) dental surgery (Cornaro, 1983; Ferrari Parabita et al., 1993; Pierleoni et al., 1993; Ragot et al., 1993, 1994; Scolari et al., 1999; Bracco et al., 2004), (d) odonto-stomatological pain (Salvato et al., 1984; Bucci et al., 1987; Moniaci et al., 1988) and (e) a range of post-operative conditions (Stefanoni et al., 1990; Ramiella et al., 1993; Binning, 2004). In the dental pain model nimesulide demonstrates rapid onset of action and is more potent than comparable doses of mefenamic acid and placebo (Fig. 12) (Ragot et al., 1994). In this model it is of interest to note that the pain-relief (measured as Pain Intensity Difference (PID) Scores were the same over the time interval up to 6hrs following 100mg compared with 200mg nimesulide, suggesting there the 100 mg dose is adequate (Pierleoni et al., 1993). These observations can be related to the non-linear plasma kinetics of the drug which deviates above 100mg dosage (Bernareggi, 1998).

In all the studies involving investigation of acute pain nimesulide has been as effective as effective as the most widely used NSAIDs (e.g. naproxen, ibuprofen, diclofenac, mefenamic acid and celecoxib and rofecoxib) where it frequently showed superior or similar efficacy but with evidence of a better GI tolerability (Bianchi and Brogini, 2002, 2003).

RAPID RELIEF OF PAIN IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE BY NIMESULIDE

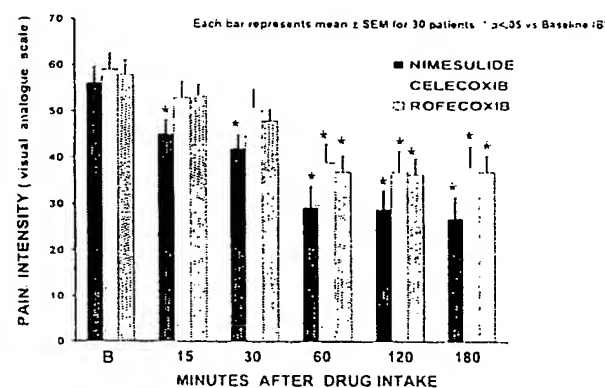


Fig. 13. Onset of pain relief in knee osteoarthritis from oral nimesulide compared with celecoxib and rofecoxib. From Bianchi and Brogini (2003).

2. Pain and Joint Inflammation in Osteoarthritis

NSAIDs are among the mostly widely-used drugs for the symptomatic treatment of painful osteoarthritis (Kean and Buchanan, 2005). The recommendations for therapy of pain and joint inflammation in this condition by the American College of Rheumatology. Subcommittee on Osteoarthritis Guidelines in 2000 (Kean and Buchanan, 2005) state that:

1. Paracetamol may give pain relief in mild osteoarthritis, but NSAIDs are more effective.
2. NSAIDs are superior to paracetamol in more severe osteoarthritis.
3. Paracetamol can be dangerous in patients with a history or current alcohol abuse or other liver injury.
4. Paracetamol can (in high doses) cause GI bleeds and ulcers.

Thus, NSAIDs are considered as a valid alternative to the first choice treatment, paracetamol, with particular reference to flares up when the first choice treatment may result inadequate. The critical point is to choose an NSAID with a low GI risk. This is where nimesulide has a place in therapy of osteoarthritis.

As noted earlier nimesulide has been found to have relatively rapid onset of analgesic action in hyperalgesia in humans when compared with well-established NSAIDs such as diclofenac and the two coxibs, celecoxib and rofecoxib (Bianchi and Brogini, 2002). In osteoarthritis, nimesulide also has a rapid onset of analgesia in comparison with the celecoxib and rofecoxib (Fig. 13) (Bianchi and Brogini, 2003).

In addition to producing rapid pain relief, the action of nimesulide in arthritic joints such as the inhibitory activity on COX-2 and NO activity, the prevention of cytokine-induced cartilage degradation compared with other NSAIDs, the oxyradical-scavenging activity, and inhibitory effects on apoptosis give a credible basis for the use of nimesulide in osteoarthritis (OA) and other musculoskeletal joint diseases and trauma states in relation to effects on joint functions (Rainsford et al., 2002, 2005; Bianchi et al., 2005). Aside from this

pharmacological rationale there is also a large amount of data on the clinical effectiveness of nimesulide have been obtained from studies in a variety of experimental designs, among them placebo-controlled and double blind studies and large-scale including post-marketing evaluations (Fossaluzza and Montagnani, 1989; Pochobradsky et al., 1991; Bardi et al., 1992; Dreiser and Riebenfeld 1993b; Estevez et al., 1993; Bourgeois et al., 1994; Lucker et al., 1994; Quattrini and Paladin, 1995; Porto et al., 1998; Roy et al., 1999; Sharma et al., 1999; Huskisson et al., 1999; Zgradic, 1999; Kriegel et al., 2001; Fioravanti et al., 2002; Bianchi and Broggin, 2003; Herrera and Gonzales, 2003; Omololu et al., 2005; Bianchi et al., 2005).

In these studies nimesulide significantly reduced the signs and symptoms of OA with an efficacy at least comparable to the reference drugs, including etodolac (Lucker et al., 1994), diclofenac (Estevez et al., 1993; Porto et al., 1998; Huskisson et al., 1999; Zgradic, 1999; Omololu et al., 2005), ketoprofen (Dreiser and Riebenfeld, 1993b), naproxen (Fossaluzza and Montagnani, 1989; Quattrini and Paladin, 1995; Kriegel et al., 2001; Fioravanti et al., 2002), piroxicam (Dreiser and Riebenfeld, 1993b; Sharma et al., 1999) as well as the coxibs, celecoxib (Bianchi and Broggin, 2003) and rofecoxib (Bianchi and Broggin, 2003; Bourgeois et al., 1994)). Of particular importance is that several studies (Bardi et al., 1992; Bourgeois et al., 1994; Porto et al., 1998; Wober, 1999) have shown the relative safety of the drug, especially in relation to the gastrointestinal tract (Porto et al., 1998) and economic advantages (Liaropoulos, 1999; Tarricone et al., 2001) of nimesulide in the treatment of osteoarthritis as well as other musculo-skeletal conditions (Wober, 1999; Pohjolainen et al., 2000).

3. Primary Dysmenorrhoea

The use of NSAIDs in the treating primary dysmenorrhoea is particularly indicated as this painful condition is directly linked to modification in prostaglandin production and affects over 50% of all menstruating women (Ylikorkala and Dawood, 1978; Jamieson and Steege, 1996; Harlow and Park, 1996; Smith, 1997; Coco, 1999). NSAIDs are well established therapies for the relief of menstrual cramps and other symptoms of primary dysmenorrhoea (Coco, 1999; Dawood, 1988, 1993; Stones and Mountfield, 2000). In a number of studies nimesulide has been found to reduce pain and menstrual symptoms (Moggian et al., 1986; Pulkkinen, 1987, 2001; Lopez Rosales et al., 1989; Pulkkinen et al., 1992; Pirhonen et al., 1995; Melis et al., 1997; Facchinetti et al., 2001). Moreover, studies in more than 1400 women, over 1000 of which treated with nimesulide, widely document the activity of nimesulide in decreasing the intrauterine pressure. Doppler assessment of arterial blood flow and the reduction of $PGF_{2\alpha}$; the latter plays a key role in the pain perception (Pulkkinen, 1987; Pulkkinen, et al. 1992; Pirhonen and Pulkkinen, 1995). Rapid onset of pain relief was observed with nimesulide in comparison with other NSAIDs, e.g. diclofenac (Facchinetti et al., 2001).

4. Headache, ENT Infections, Fever and Minor Pain States

Like other NSAIDs (Rainsford, 2004b) nimesulide has well documented evidence for relieving symptoms associated

with migrainous and non-migraine headaches, upper respiratory tract, ear nose and throat infections with associated fever, as well as in minor pain states (Reiner and Massers, 1984; Reiner et al., 1985; Antonelli et al., 1993; Cuniatti et al., 1993; Giacobazzo et al., 1993; Zuckermann et al., 1993; Goyal et al., 1998; Neimark et al., 2004) (also reviewed in Bianchi et al., 2005). A particular advantage in the respiratory conditions is the relatively low likelihood of asthmatic and other allergic reactions with nimesulide (Bianco et al., 1993; Senna et al., 1996; Bianchi et al., 2005).

5. Cancer Pain

NSAIDs represent the first step in the World Health Organization guideline for stepwise analgesia in cancer pain (Rainsford, 2004b). Nimesulide has been shown to have analgesic activity in various cancer pain states, with activity that is comparable with that of established NSAIDs such as diclofenac and naproxen (Ventafredda et al., 1990; Gallucci et al., 1992; Corli et al., 1993; Toscani et al., 1993). Of particular value is the use of the suppository formulation of nimesulide which as shown in a study by Corli et al. (1993) to have a rapid onset and sustained pain relief.

There is much interest in the potential for NSAIDs to prevent the development of cancer (Ulrich et al., 2006). Recent studies in experimental models suggest that nimesulide may have the potential for cancer chemoprevention in colorectal and lung cancers (Rainsford, 2005a), head and neck cancer (Lin et al., 2002) and from topical application in oral cancers (Sood et al., 2005). There are multiple actions of nimesulide on cancer cells including its inhibitory effects on COX-2 activity, signal transduction pathways, angiogenesis and selective activation of apoptosis that may be implicated in arresting cancer cell growth and prevention of the spread of tumours (Rainsford, 2005a). A recent report indicated that nimesulide has inhibitory effects on oestrogen metabolism by aromatase activity in breast cancer cells which may have significance for prevention of breast cancer (Brueggemeier et al., 2005).

5. Conclusions

The extensive studies and over 20 years of successful clinical use of nimesulide in treating musculo-skeletal and acute and chronic pain states has shown the drug exhibits rapid and sustained control of inflammation and pain.

Adverse Reactions and Relative Safety

Several reviews have been published in recent years on the adverse reaction profile of nimesulide in comparison with that of other NSAIDs (Rainsford, 1996, 1998, 1999b, 2001; Bianco et al., 1993; Senna et al., 1996; Conforti et al., 2001; Lanos 2001; Boelsterli, 2002a, 2000b; Traversa et al., 2003; Laporte et al., 2004). These studies show that nimesulide has, overall, a pattern of organ reactions similar to that from other NSAIDs, though there are quantitative differences in the incidence of adverse reactions.

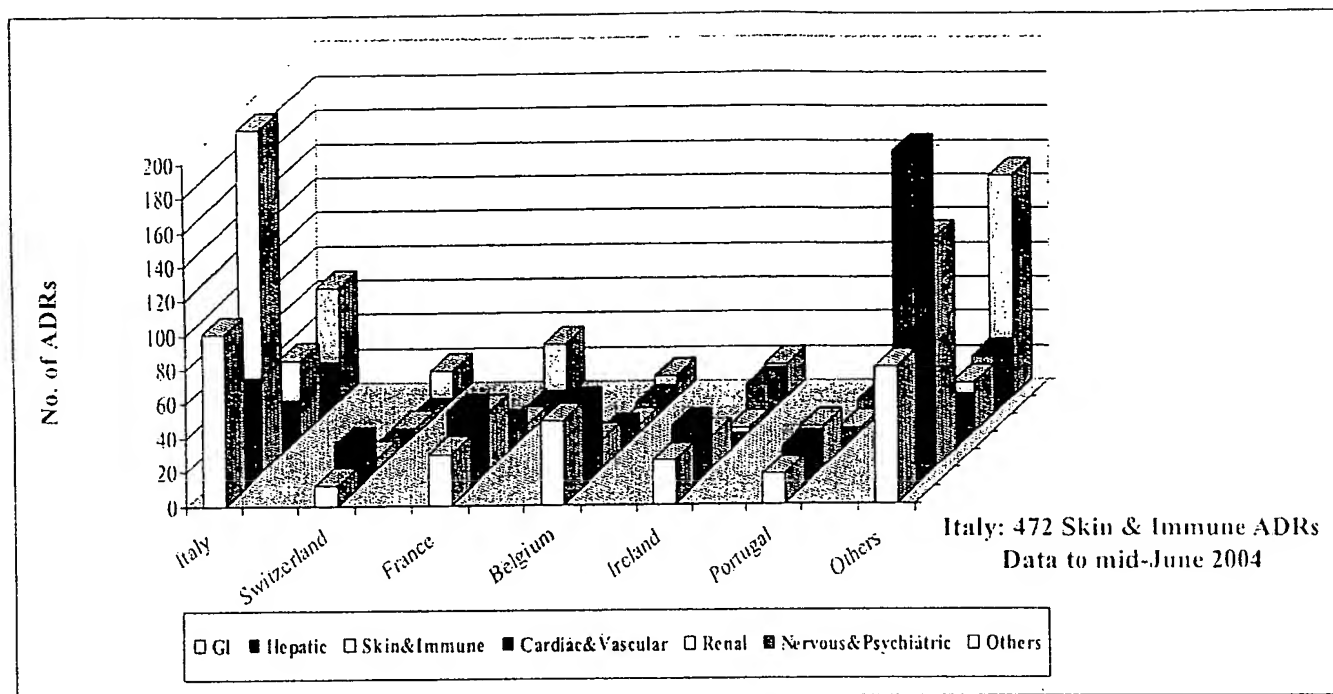


Fig. 14. Adverse Drug Reactions (ADRs), both serious and non-serious, from nimesulide by body system reported in the main countries where this drug has been marketed. From Bjarnason et al. (2005).

A comprehensive review was recently undertaken by Bjarnason and co-workers (2005) of all aspects of the relative safety and the mechanisms that are understood to underlie the adverse reactions from nimesulide. The data reviewed was derived from (a) epidemiological studies, (b) spontaneous reports of adverse drug reactions (ADRs) reported to Helsinn Healthcare SA, the WHO Nimbus Database and in published reports, (c) controlled clinical investigations in human volunteers and patients, (d) studies in laboratory animal models *in vivo* involving conventional toxicological and bioassays or pharmacological investigations designed to establish mode of action in relation to known adverse events (e.g. gastric acid secretion, parameters of renal function), and (e) *in vitro* studies in cellular or tissue systems, molecular biological and biochemical and molecular studies investigating mechanisms of toxic reactions or physiological functions in target organs wherein adverse events are known to occur. Detailed review of these investigations is found in Bjarnason et al. (2005) to which the reader is referred. Here the principal observations of the adverse reactions and toxic effects in the major organ systems are summarized thus:

(1) Overall pattern of adverse reactions

Figure 14 shows the overall pattern of serious adverse reactions in the main countries where nimesulide has been marketed by Helsinn Healthcare SA since the introduction of the drug in 1985. The majority of reactions have been in the skin and immune systems with fewer being evident in the GI, hepatic and renal systems; this is at variance with the pattern observed with classical NSAIDs, where ADRs

in the GI system usually predominate (Rainsford and Velo 1984, 1985; Rainsford, 1996, 1998, 1999a, 2001; McGettigan et al., 2000; Lanas, 2001; Laporte et al., 2004).

(2) Gastrointestinal tract:

Serious GI events from nimesulide are rare; in the past 5 years these have averaged 1.1 cases per 10^6 treatment courses (Bjarnason et al., 2005). Serious GI ADRs comprise 15.7% of all reports of which 4.4% were fatal but possibly not due to the drug. Pharmacoepidemiological studies in case-control, cohort or hospitalization studies have given risk assessments (Relative Risk or Odds Ratios) of 1.2, 2.0 and 4.0 respectively with reference drugs excepting ibuprofen (for which the values are comparable) exceeding these by 2–5 fold.

Gastro-duodenal endoscopy and intestinal permeability studies have shown that nimesulide 100 mg b.i.d. produces little if any GI damage (Bjarnason and Thjodleifson, 1999). This contrasts with naproxen 500 mg b.i.d. or other conventional NSAIDs, which all produce visual evidence of gastroduodenal damage and with the former increased intestinal permeability and inflammation. As noted earlier in the section on pharmacological studies these low GI effects of nimesulide can be related to sparing of gastric mucosal and plasma COX-1 combined with its properties of controlling histamine release from mast cells, apparent anti-acid secretory activity, inhibitory effects on leucocyte emigration and activation, antioxidant activity and possibly effects on the production and actions of proinflammatory cytokines. Data from studies in experimental animal models strongly

supports the epidemiological data showing that nimesulide has a relatively low risk of serious GI reactions especially in comparison with other NSAIDs.

(2) Hepatic

Hepato-biliary disorders associated with nimesulide account for 14.3 % of all serious ADRs, while abnormal laboratory findings comprise 6.6 % of these, principally abnormal liver function tests. Like other NSAIDs, nimesulide is infrequently associated with elevation of the liver transaminases (ALT, AST, γ -GT), and less so with liver function tests (ALP, free and conjugated bilirubin) and, rarely, cholestatic jaundice. In most cases cessation of the drug results in restoration to normal of elevated liver transaminases and liver function tests (Bjarnason et al., 2005).

In pharmaco-epidemiological studies (Traversa et al., 2003) the occurrence of hepatopathy from nimesulide is at the upper end of the range compared with NSAIDs. The relative risks are in the range of 1.3–1.4. Most cases have confounding factors (other hepatotoxic drugs or liver diseases) (Rainsford, 1998, 1999b; Boelsterli et al., 2002a, 2002b). High concentrations (up to 100 μ mol/L) of nimesulide, its metabolites and manufacturing impurities have not been found to cause direct cytotoxic damage to liver cells in culture (Rainsford et al., 2001), although increased cell damage is evident when paracetamol or other hepatotoxic drugs are present (K D Rainsford, unpublished studies). Thus it is unlikely that the drug or its metabolites have direct actions on liver cells. It is possible that the liver reactions attributed to nimesulide are idiosyncratic (Boelsterli, 2002b). Considerable evidence exists to show that most liver ADRs have been in patients that have taken hepatotoxic drugs and/or have liver diseases.

The formation of nitroso or hydroxylamine reactive metabolites of nimesulide has been suggested to be responsible for the liver damage from the drug (Boelsterli, 2002b), like that of reactive metabolite injury from diclofenac, paracetamol and other hepatotoxins (Boelsterli, 2002a). There is no evidence to support this reactive metabolite hypothesis of cell injury by nimesulide. Reduction in mitochondrial ATP and other functions has been observed with nimesulide following administration of high doses of the drug to rats. This phenomenon is related to uncoupling of oxidative phosphorylation like that observed with acidic NSAIDs and might account for the development of liver injury by these drugs. Reduction in ATP may initiate apoptosis by these drugs.

(3) Renal

Renal and urinary tract disorders comprise 4.7 % of all ADRs reported and are rare. These resemble those encountered with other NSAIDs (Bjarnason et al., 2005) They include tubular and interstitial nephritis, nephritic syndrome and renal failure.

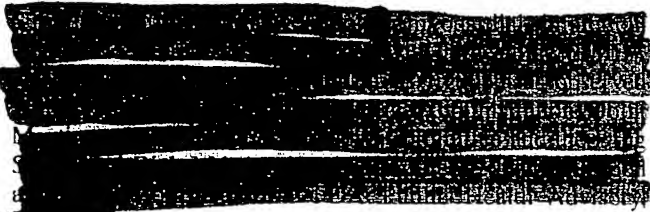
Inhibition of renal prostaglandin production accounts for the transient physio-pathological renal effects of the drug on electrolyte balance, water impairment, and renin production; these being similar to those of other NSAIDs. Renal

ADRs that appear in the elderly are related to impaired renal clearance of the drug.

(4) Cutaneous and allergic reactions

Nimesulide is frequently associated with minor skin reactions (erythematous rashes, urticaria etc); these being akin to those with other NSAIDs (Rainsford, 1992) Stevens-Johnson and Lyell's syndromes have been rarely reported; the occurrence of these reactions may be lower than observed with other NSAIDs. Intolerance to nimesulide is rare in patients with pseudo-allergic reactions to other NSAID and aspirin-sensitive asthmatic patients (Bianco et al., 1993; Senna et al., 1996).

(5) Cardiovascular system

 Mild blood pressure changes have been observed with nimesulide (Rainsford, 1999) and this is also observed with most NSAIDs and could be related to COX-2 inhibition (Khanna et al., 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b).

(6) Role of Pharmacokinetics

The role of pharmacokinetics of nimesulide in determining adverse reactions and toxicity has been reviewed (Rainsford, 1999b; Bernareggi and Rainsford, 2005). The likelihood of drug accumulation upon repeated dosage (i.e. after steady state levels of the drug have been achieved at 7 days) in elderly patients without hepato-renal conditions is rare. As shown in Figure 18 the clearance and volume of distribution of nimesulide is unaffected by age. Furthermore, there are no differences in pharmacokinetic parameters between the sexes (Fig. 19) (Bernareggi and Rainsford, 2005) such as observed with some NSAIDs (e.g. the salicylates (Rainsford, 1996, 2004). Of the drug interactions those affecting pharmacokinetics include the reduction by nimesulide in the bioavailability of furosemide when taken with nimesulide concomitant with reduction in the natriuretic and, to a lesser extent, the kaliuretic effects of this drug (Bernareggi and Rainsford, 2005). The pharmacokinetics of warfarin, digoxin (in patients with mild congestive heart disease), theophylline and glybenclamide are mostly unaffected by nimesulide and vice versa (Bernareggi and Rainsford, 2005). Prothrombin times during treatment with warfarin or acenocoumarol are unaffected by nimesulide (Rainsford, 1999b). Reduced plasma levels of theophylline have, however, been found in

patients with chronic obstructive lung disease that received nimesulide (Rainsford, 1999b). Cimetidine and antacids do not affect the bioavailability of nimesulide (Bernareggi and Rainsford, 2005) possibly because the ionisation of the drug in the stomach is not an issue for its absorption. Some drugs affect the protein binding of nimesulide but probably these are not sufficient to be of clinical significance. These observations suggest that there are few significant drug interactions between nimesulide and other drugs that may be taken by patients with osteoarthritis or other musculo-skeletal conditions.

Benefit/risk profile

Based on what has been discussed above the following conclusions can be drawn on the overall benefit/risk profile of nimesulide.

The therapeutic benefits of nimesulide have been compared with both placebo and the most widely used NSAIDs for the main approved indications, including acute pain, treatment of painful osteoarthritis and primary dysmenorrhoea. Nimesulide proved to be a valid alternative to other NSAIDs, with a similar or even superior clinical efficacy characterized by a fast onset of action.

As evident in the safety section, nimesulide shares the characteristic side effects of NSAIDs, such as GI, skin, renal, hepatic reactions. Like other drugs in the class, the occurrence of adverse reactions suggesting hypersensitivity comprises a significant proportion of the total reactions. Analysis of the incidence of all adverse reactions from the available data confirms this to be in line with the class. In particular it can be affirmed that the incidence of upper GI perforation, bleeding and ulceration is low and that nimesulide is probably less prone to produce gastrointestinal bleeding than other NSAIDs. Incidence rate is similarly low for renal, serious skin and hepatic reactions.

Data on post marketing surveillance confirms that there is not signal of any changes in the clinical characteristics of listed serious and non-serious adverse reactions overtime or of any potentially 'new' adverse reactions or new signals related to nimesulide. This, together with the evidence from clinical studies, allows confirming that the favourable and invariant benefit risk profile of nimesulide.

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
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The Pain Market Outlook to 2011

By Melissa Zebrowski

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...REPORTS...

Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis: Data From the Third National Health and Nutrition Examination Survey

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Abstract

Objective: To estimate the prevalence of traditional risk factors for cardiovascular disease (CVD) among US adults with osteoarthritis (OA).

Methods: Using survey data from the Third National Health and Nutrition Examination Survey, we estimated the prevalence of selected CVD risk factors among a US OA and nonarthritic adult population. In additional analyses, we stratified the sample by gender and age (35-44, 45-64, and 65+ years) to further understand the CVD risk profile in an arthritic population and nonarthritic population. Relevant data on each survey participant's demographics, arthritis status, CVD risk factors, and sampling weights were obtained from the survey database.

Results: Of the 115.9 million US adults aged ≥ 35 years, 24.3 million (21%) have OA. Hypertension is prevalent in approximately 40% of OA patients; 20% of the patients smoke and 11% have diabetes. Prevalence of high total cholesterol is estimated to be 32%, while prevalence of low high-density lipoprotein cholesterol is estimated at 13%. Approximately 37% of OA patients are estimated to have renal impairment, but less than 1% suffer from renal failure.

Conclusion: National survey data suggest that, on average, US adults with OA have a high prevalence of cardiovascular risk factors. These findings highlight the need to consider patients' comorbidities when selecting the appropriate treatment options.

(*Am J Manag Care.* 2002;8:S383-S391)

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Arthritis is a widely prevalent, disabling disease that places substantial demands on healthcare resources. It has been estimated that as many as 44

million outpatient visits and three quarters of a million hospitalizations annually are attributable to arthritis and its treatment, with associated direct medical care costs of \$15 billion.^{1,2} Estimates of lost productivity and other indirect costs of arthritis have been estimated to be as high as \$50 billion annually.^{1,2} The clinical and economic burdens of arthritis in the United States are expected to increase as the general population ages; an estimated 60 million Americans (nearly 20% of the population) are projected to have arthritis by 2020; of whom approximately one fifth (or 12 million people) will experience meaningful activity limitation.^{1,3-5}

There is credible evidence that people with osteoarthritis (OA) and rheumatoid arthritis (RA) are at higher risk than the general population for several comorbid conditions, particularly cardiovascular disease (CVD).⁶⁻⁸ Moreover, there is an established body of research suggesting that age-adjusted mortality risk is higher among RA patients relative to the general population.⁷⁻¹⁷

The etiology of the association between arthritis and CVD is not fully understood. Various theories about the relationship have been put forth in recent studies, most of which are based on the premise that patients with arthritis are at advanced risk for development of CVD by virtue of their unfavorable risk factor profile. However, there is inherent difficulty in sorting out the relevant causes of CVD

in arthritis patients as they differ from the general population in many aspects. Changes in body mass composition, changes in lipid profile associated with medication use (eg, glucocorticoids), and activity limitations resulting from chronic joint disease may all play a role in increased CVD risk.^{18,19} Some investigators believe that vascular inflammation associated with increased levels of thiol compounds and C-reactive protein, as well as peroxidization of low-density lipoprotein, may play a significant role in CVD pathogenesis in patients with arthritis.^{18,20} Medications taken for arthritis-related conditions have also been implicated for either directly or indirectly leading to atherosclerosis.^{18,21,22} The most commonly implicated drugs are glucocorticoids (chiefly, prednisone), which can increase serum lipids and glucose levels and induce hypertension.²³ Methotrexate, another commonly prescribed arthritis medication, has been shown to increase serum homocysteine levels.^{23,24}

Although national estimates of OA and RA prevalence have been reported,^{1,3,4} to the best of our knowledge the prevalence of CVD risk factors among such people has not been estimated to date. To this end, the government-sponsored database on the health status of the US population—the Third National Health and Nutrition Examination Survey (NHANES III)—was used to develop national estimates of the prevalence of selected cardiovascular risk factors among adult patients with self-reported OA and a nonarthritic US adult population.

...MATERIALS AND METHODS...

Data Source

We estimated the prevalence of selected CVD risk factors among US adults aged ≥ 35 years by diagnosis, gender, and age category (35-44, 45-64, and 65+ years) using survey data from NHANES III.²⁵

NHANES is one of the major programs in the series of health-related studies conducted by the National Center for Health Statistics, part of the US Centers for

Disease Control and Prevention, over the past 35 years. NHANES is designed to assess the health and nutritional status of adults and children in the United States through interviews and direct physical examinations. The survey is unique in that it combines a home interview with physical examinations and a variety of diagnostic and laboratory tests conducted in a mobile examination center. NHANES III, which was conducted from 1988 to 1994, included approximately 40 000 people aged ≥ 2 months selected from households in 81 counties across the 50 US states. Using a complex, stratified, multistage probability cluster sampling design (with oversampling of young children, older people, blacks, and Mexican Americans), the survey yields nationally representative information on the health and nutritional status of the civilian, non-institutionalized US population. Physical examinations and objective measures are employed when information cannot be furnished or is not available in a standardized manner through interviews or through records maintained by the health professionals who provide medical care to survey respondents.²⁵⁻²⁷

The 4 data files representing the major components of NHANES III are adult household, examination, laboratory, and dietary recall; more than 5000 data elements are collected. One section of the household adult questionnaire asks respondents to note whether a physician has told them that they have OA or RA, and when they were first told that they had the condition. Other sections of the questionnaire focus on diabetes, high blood pressure, CVD, musculoskeletal conditions, gallbladder disease, kidney conditions, respiratory and allergy conditions, vision and hearing, and dental care. Histories of smoking and chewing tobacco use are recorded on both the home adult questionnaire and examination questionnaire, while history of alcohol use is asked on the examination questionnaire. Other NHANES sections pertain to exercise, nutrition assessment, medicine/vitamin use, biochemistry values, and physical examination results. Biochemistry data collected con-

sist of hematologic tests, general biochemistry tests, urine tests, antibody tests, and diabetes testing profile. The physical exam consists of a physician's exam, dental examination, allergy skin test, audiometry, spirometry, bone densitometry, gallbladder ultrasonography, and fundus photography.^{25,26}

CVD risk factors examined in this study, as derived from the Household Adult Questionnaire (HAQ) and Laboratory Data File components of the NHANES III database, include systolic blood pressure (SBP) and diastolic blood pressure (DBP), total and high-density lipoprotein (HDL) cholesterol, physician-diagnosed diabetes mellitus, renal impairment or failure based on serum creatinine levels, and current cigarette smoking. Arthritis status was derived from the arthritis section of the HAQ as described above. Smoking status was derived from the question, "Do you smoke cigarettes now?" Diabetes mellitus status was derived from questions asking respondents whether a doctor had ever told them that they have diabetes. All other risk factor data were obtained from the NHANES III Laboratory Data File. Hypertension as a CVD risk factor was defined as SBP >140 mm Hg or DBP >90 mm Hg, as defined by current National Institutes of Health *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI) guidelines.²⁸ Renal impairment and failure were defined respectively as serum creatinine levels exceeding the upper limit and twice the upper limit of normal (ie, >1.5 mg/dL and >3 mg/dL, respectively), which reflects the methods of the Massachusetts General Hospital.²⁹

Statistical Analyses

Prevalence (stated as percentages) and associated 95% confidence intervals (CIs) were estimated for each CVD risk factor among an OA and a nonarthritic population. Gender- and age-stratified prevalence rates were also estimated for each population. SUDAAN® statistical analysis software (Research Triangle Institute,

Research Triangle Park, NC) in conjunction with Statistical Analysis System (SAS) Release 8.02 (SAS Institute, Cary, NC) were used for these analyses. SUDAAN is specifically designed for analysis of cluster-correlated data from surveys such as NHANES III that involve multistage sample designs. Robust variance estimates are generated that account for intracluster correlation, unequal weighting, stratification, and without-replacement sampling. To provide estimates that were representative of the US population, analyses of each data element incorporated sampling weights obtained from the NHANES III database. These weights account for the unequal probabilities of selection resulting from the cluster design, the planned oversampling of certain demographic subgroups, and nonresponse adjustment factors based on US Census Bureau data on age, gender, race, income, and geographic location of the US population.^{26,27} Since our investigation focused on interval estimation rather than on hypothesis testing, no tests of statistical significance were undertaken.

...RESULTS...

Prevalence Estimates

Osteoarthritis. Of the 115.9 million US adults aged ≥35 years, 24.3 million (21%) have OA (95% CI, 22.1 million-26.6 million) (Table 1). Nearly two thirds of these people are women. Prevalence rates of OA increase with age in both genders. However, the ratio of females to males with OA increases with advancing age, from 1.32:1 among people aged 35 to 44 years to 1.88:1 among people aged ≥65 years.

Table 1 also shows that the nonarthritic population is considerably younger than the OA population. Over 47% of OA patients are older than 65 years, compared with only 19% of those in the nonarthritic population. In addition, there were gender differences between the arthritis and nonarthritic populations; nearly 63% of the OA population was comprised of women, compared with only 49.9% of the general nonarthritic population.

Table 1. Estimated Numbers of US Adults Aged ≥ 35 Years With Osteoarthritis, by Gender and Age

Gender and Age (Years)	Osteoarthritis		General Population Without Arthritis	
	Percentage of People (95% CI)		Percentage of People (95% CI)	
All (n)	24 345 370	(22 110 212-26 580 528)	85 800 548	(78 999 986-92 601 110)
35-44	13.30	(11.79-14.56)	41.41	(40.18-42.47)
45-64	39.49	(39.26-39.68)	39.59	(39.74-39.46)
65+	47.21	(45.01-49.04)	18.99	(17.85-19.97)
Men (n)	9 015 680	(7 874 587-10 156 773)	42 986 882	(39 689 389-46 284 375)
35-44	15.51	(12.70-17.69)	40.13	(38.36-41.65)
45-64	40.23	(38.75-41.38)	41.17	(41.02-41.30)
65+	44.26	(42.54-45.59)	18.70	(17.63-19.62)
Women (n)	15 329 690	(13 824 691-16 834 689)	42 813 666	(38 878 456-46 748 876)
35-44	12.00	(9.99-13.66)	42.70	(41.43-43.77)
45-64	39.05	(37.58-40.26)	38.01	(37.44-38.48)
65+	48.95	(46.67-50.82)	19.29	(17.81-20.52)

CI indicates confidence interval.

Hypertension. Approximately 40% (95% CI, 35.3-45.5) of people with OA have Stage I-III hypertension as defined by the JNC VI guidelines (Table 2).²⁸ By comparison, only about 25% (95% CI, 23.0-27.6) of the general population without arthritis was estimated to have hypertension. Prevalence of hypertension is slightly higher among men than women, and, as epidemiologic data suggest, higher among people aged ≥ 65 years versus younger people.

Cigarette Smoking. Approximately 20% (95% CI, 17.6-23.1) of OA patients are current cigarette smokers (Table 2). The crude rates in this analysis are slightly lower than that for the general population without arthritis, wherein about 26% (95% CI, 23.6-28.4) are smokers.

Diabetes Mellitus. Approximately 11% (95% CI, 9.2-12.9) of people with OA have diabetes mellitus (Table 2). By comparison, only about 6% (95% CI, 5.6-7.3) of the general population without arthritis is diabetic. When stratifying by gender, this analysis suggests that female OA patients were more likely to have diabetes mellitus than a nonarthritic population. Prevalence of diabetes is slightly higher among

women than men, and, as epidemiologic data suggest, higher among older people.

Hypercholesterolemia. Approximately 32% (95% CI, 27.1-36.2) of people with OA have high total cholesterol levels (ie, ≥ 240 mg/dL) (Table 2). About 24% (95% CI, 21.4-26.0%) of the general population without arthritis has high total cholesterol levels. Prevalence of high total cholesterol is slightly greater among women than men, and has a marked increase among people aged 45 years and older.

Low HDL Cholesterol. The prevalence of low HDL cholesterol (< 35 mg/dL) is similar, approximately 13% (95% CI, 10.8-16.1) in people with OA and 12% (95% CI, 10.4-13.2) in the general population without arthritis (Table 2). Prevalence of low HDL cholesterol is substantially higher among men than women, but there is little differentiation among the age categories.

Renal Impairment and Failure. Approximately 37% (95% CI, 31.6-41.5) of people with OA have renal impairment, manifested as serum creatinine levels exceeding the upper normal limit of 1.5 mg/dL (Table 2). Moreover, approximately 0.8% (95% CI, 0.4-1.3) of people with OA

Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis

have renal failure, defined as serum creatinine levels exceeding twice the upper normal limit (ie, ≥ 3.0 mg/dL). By comparison, it is estimated that only about 27% (95% CI, 23.8-30.3) of the general population without arthritis have renal impairment, and only 0.3% (95% CI, 0.2-0.4) have renal failure.

DISCUSSION

Patient-level examination data from the NHANES III have been used to estimate the prevalence of selected CVD risk factors among US adults with OA. Other studies assessing the prevalence of arthritis in the United States have been conducted, but the prevalence of traditional risk factors for CVD among arthritis patients has not been well quantified to date.

Estimates suggest that approximately 24.3 million US adults aged ≥ 35 years have OA, and that nearly two thirds of these people are women. These estimates are consistent with what has been reported elsewhere.³

Findings suggest that US adults with OA indeed may be at an increased risk of CVD relative to the nonarthritic population. For each of the risk factors examined, except cigarette smoking, point estimates of prevalence among OA patients exceeded those of the general population. While tests of statistical significance were not performed, it was observed that the difference-in-risk factor-prevalence versus the general population is not statistically significant at the "conventional" $\alpha = 0.05$ level.

Our findings suggest that the prevalence of hypertension is significantly greater among OA patients versus patients without arthritis. Gabriel and colleagues⁶ found the prevalence of diabetes to be 5.0% among 441 OA patients. The estimates from this study at 11% are considerably higher. This difference could be related to a different population sampling in the 2 studies.

Reports on total cholesterol levels among patients with arthritis are scant

Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥ 35 Years With and Without Osteoarthritis

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)	Prevalence, % (95% CI)			
	Osteoarthritis (n = 24 345 370)		General Population Without Arthritis (n = 115 861 005)	
Hypertension (Stage I-III, JNC VI Guidelines*)				
All	40%	(35.3-45.5)	25%	(23.0-27.6)
35-44	14%	(7.5-19.7)	11%	(9.3-13.1)
45-64	32%	(26.4-37.3)	28%	(24.6-31.5)
65+	55%	(46.8-63.5)	50%	(42.9-57.8)
Men	41%	(33.4-47.7)	28%	(25.1-31.0)
35-44	20%	(6.8-33.1)	14%	(11.1-17.7)
45-64	33%	(22.1-43.5)	32%	(27.4-36.7)
65+	55%	(45.5-64.2)	49%	(41.2-56.0)
Women	40%	(34.9-45.7)	23%	(19.8-25.4)
35-44	9%	(2.8-14.8)	8%	(6.1-10.3)
45-64	31%	(25.1-37.3)	24%	(20.2-27.2)
65+	55%	(45.7-64.8)	52%	(41.8-62.6)
Cigarette Smoking				
All	20%	(17.6-23.1)	26%	(23.6-28.4)
35-44	25%	(16.1-34.5)	31%	(27.2-34.8)
45-64	31%	(26.1-35.9)	26%	(22.6-29.3)
65+	10%	(8.1-12.2)	15%	(12.3-17.8)
Men	25%	(19.5-29.9)	30%	(26.9-33.2)
35-44	34%	(13.5-54.2)	36%	(30.7-42.3)
45-64	35%	(24.6-44.7)	29%	(24.5-34.2)
65+	12%	(8.2-16.6)	18%	(13.4-22.1)
Women	18%	(15.2-20.5)	22%	(19.1-24.7)
35-44	19%	(11.1-26.4)	26%	(21.4-30.4)
45-64	29%	(23.0-34.5)	22%	(18.2-26.2)
65+	9%	(6.4-11.5)	12%	(9.9-14.8)
Diabetes Mellitus				
All	11%	(9.2-12.9)	6%	(5.6-7.3)
35-44	4%	(0.7-7.2)	4%	(2.3-5.1)
45-64	11%	(7.3-13.8)	7%	(5.8-8.3)
65+	13%	(11.0-15.9)	11%	(9.0-12.8)
Men	10%	(7.3-12.3)	7%	(5.4-7.7)
35-44	0%	(-0.2-1.1)	3%	(1.0-5.3)
45-64	9%	(4.2-13.5)	8%	(6.0-10.0)
65+	14%	(9.8-18.1)	11%	(8.8-13.2)
Women	12%	(9.5-14.1)	6%	(5.0-7.5)
35-44	7%	(1.0-12.4)	4%	(2.6-6.1)
45-64	12%	(7.6-15.7)	6%	(4.4-7.7)
65+	13%	(10.3-16.1)	11%	(7.9-13.8)
High Total Cholesterol (≥ 240 mg/dL)				
All	32%	(27.1-36.2)	24%	(21.4-26.0)
35-44	22%	(11.6-32.5)	15%	(12.9-17.5)
45-64	34%	(27.8-39.3)	29%	(26.0-31.9)
65+	33%	(26.3-39.3)	31%	(25.9-36.7)
Men	23%	(17.7-28.5)	23%	(20.2-25.6)
35-44	22%	(10.5-33.9)	19%	(15.7-22.5)
45-64	26%	(18.6-33.4)	27%	(23.4-31.0)
65+	21%	(13.9-27.6)	21%	(17.1-25.7)
Women	37%	(30.9-42.7)	24%	(21.8-27.1)
35-44	22%	(8.9-35.0)	12%	(9.2-13.9)
45-64	38%	(29.9-46.5)	31%	(27.2-34.5)
65+	39%	(31.4-47.3)	41%	(32.8-49.2)

(continued on next page)

*Systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg (NIH Publication 98-4080, November 1997).

CVD indicates cardiovascular disease; JNC VI, Sixth Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure.

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Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥ 35 Years With and Without Osteoarthritis (*Continued*)

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)	Osteoarthritis (n = 24 345 370)		General Population Without Arthritis (n = 115 861 005)	
Low HDL Cholesterol (<35 mg/dL)				
All	13%	(10.8-16.1)	12%	(10.4-13.2)
35-44	15%	(7.9-21.5)	11%	(9.2-13.8)
45-64	14%	(10.2-17.9)	12%	(10.0-13.5)
65+	13%	(9.9-15.2)	13%	(9.8-15.6)
Men	25%	(19.3-30.9)	18%	(15.9-20.8)
35-44	29%	(12.9-44.8)	18%	(13.7-22.3)
45-64	27%	(17.6-35.6)	19%	(15.6-21.7)
65+	22%	(15.9-29.0)	18%	(14.5-22.4)
Women	6%	(5.0-7.9)	5%	(4.0-6.6)
35-44	3%	(0.1-6.6)	5%	(3.4-7.5)
45-64	6%	(4.2-8.6)	4%	(2.9-5.3)
65+	7%	(5.1-9.2)	7%	(4.2-10.2)
Renal Impairment (Serum Creatinine Levels Above ULN, 1.5 mg/dL)				
All	37%	(31.6-41.5)	27%	(23.8-30.3)
35-44	18%	(11.1-25.0)	19%	(14.9-22.7)
45-64	28%	(22.3-33.2)	27%	(23.2-30.5)
65+	50%	(42.1-57.2)	46%	(39.1-53.5)
Men	38%	(31.3-44.1)	29%	(25.8-32.8)
35-44	24%	(9.0-38.3)	22%	(16.6-26.6)
45-64	26%	(18.0-35.0)	29%	(24.5-33.8)
65+	53%	(42.8-63.4)	47%	(39.2-54.5)
Women	36%	(30.3-41.5)	25%	(21.1-28.5)
35-44	14%	(8.0-19.1)	16%	(12.5-19.8)
45-64	28%	(21.6-35.3)	24%	(19.6-28.9)
65+	48%	(39.2-56.4)	46%	(37.0-54.4)
Renal Failure (Serum Creatinine Levels $2\times$ ULN ≥ 3.0 mg/dL)				
All	0.8%	(0.4-1.3)	0.3%	(0.2-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.0-0.1)
45-64	0.2%	(0.0-0.5)	0.1%	(0.0-0.2)
65+	1.6%	(0.6-2.6)	1.0%	(0.5-1.4)
Men	1.0%	(0.2-1.8)	0.2%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.0%	(0.0-0.1)
45-64	0.3%	(-0.1-0.7)	0.2%	(0.0-0.3)
65+	2.0%	(0.1-3.9)	0.9%	(0.2-1.5)
Women	0.8%	(0.2-1.3)	0.3%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.1-0.1)
45-64	0.2%	(-0.1-0.5)	0.1%	(0.0-0.1)
65+	1.4%	(0.3-2.6)	1.0%	(0.2-1.9)

CVD indicates cardiovascular disease; HDL, high-density lipoprotein; ULN, upper limit of normal.

and somewhat contradictory. A prevalence rate of 32% was estimated in OA patients, which is higher than the 23% rate estimated for the general population. The comparatively lower prevalence of cardio-protective HDL cholesterol found in this

study is consistent with what has been reported in other studies.^{9,30-34}

Potential limitations of this study bear mention. First, it should be noted that due to the complex sampling design of NHANES III, extreme variability in the weights has the potential to result in reduced reliability of the estimates. However, the NHANES III sample was designed to minimize the variability in the weights through measures such as weight trimming. Although unlikely, extreme observations in conjunction with large weights may have resulted in extremely influential observations dominating the analyses.²⁷ Data from the NHANES surveys are considered by health services researchers to be among the most suitable-to-task for purposes of generating national estimates of disease incidence and prevalence. Nonetheless, because NHANES III is based on surveys of the civilian noninstitutionalized population, which represents 98% of the total US population, certain groups (eg, the institutionalized elderly) were excluded.³ Although the NHANES sampling methodology accounts for factors such as this, estimates of disease and risk factor prevalence presented in this article could differ somewhat from true prevalence.

Identification of comorbid medical conditions in NHANES III is derived mainly from patient self-report rather than from physical examination. Moreover, the self-reported data are confirmed by physicians only in certain circumstances. The validity of using self-reports of arthritic conditions to estimate true prevalence of OA is unknown, but studies conducted in other disease areas suggest that self-reported measures selected from NHANES can be quite reliable. The sensitivity and specificity of self-reported hypertension in NHANES III has been assessed,³⁵ and the validity of using NHANES data in this fashion for surveillance of hypertension trends in the US population is well established. Also, self-reports of an arthritis diagnosis derived from NHANES data have been used to examine the association between arthritis incidence and use of estrogen replacement therapy, body mass index,

and weight change,^{36,37} and to explore associations between arthritis diagnosis, educational attainment, and mortality.³⁸⁻⁴⁰

Because many people with arthritis may not consult a physician for their condition, they consequently may not be able to affirmatively answer the NHANES question regarding whether a doctor has told them they have arthritis. Furthermore, the possibility of faulty recall or other ascertainment bias among NHANES III participants cannot be ruled out. Patients whose health histories span many years may omit less serious health conditions, misplace dates of occurrence, or incorrectly remember the names of health conditions that were diagnosed several months or years in the past. Certainly, poor communication or a lack of understanding of medical terminology could be detrimental factors. Patients mistaking "rheumatism" for "rheumatoid arthritis" could be one example. A related concern is that the terms used to name or describe a given health condition vary among people of different language, cultural, social, or educational backgrounds. Compounding this problem is the fact that NHANES uses a checklist to collect information on chronic conditions and does not include definitions of the terms or lists of related symptoms to provide a consistent definition across subjects. However, NHANES has a deserved reputation for its clear, unambiguous diagnostic criteria and wording on its questionnaires. Although the self-reported information regarding arthritis in NHANES III has not been systematically validated, NHANES patient data has been used to ascertain prevalence of chronic disease, including arthritis, with wide acceptance since the 1970s. Self-reported rheumatoid arthritis was excluded from this analysis because it is unlikely that patients would be able to reliably report this diagnosis for all the reasons listed above.

Finally, one of the major limitations of this study was the relatively limited number of CVD risk factors that could be estimated using the NHANES III database. Interestingly, McEntegart and colleagues⁹ and Wällberg-Jonsson and colleagues^{18,41}

in their studies of RA patients identified significant correlations between RA and several thrombotic predictors of CVD that we were not able to derive from NHANES III data, including fibrinogen, von Willebrand factor, plasminogen activator inhibitor 1, tissue plasminogen activator antigen, and fibrin D-dimer. Current thinking is that inflammatory factors that promote atherogenesis and thrombogenesis may play important roles in the development of CVD in arthritis patients, particularly those with RA. Had it been possible, estimation of prevalence rates for these potential risk factors would have been worthwhile.

...CONCLUSION...

National survey data suggests, on average, US adults with OA have a high prevalence of CVD risk factors, which is higher than that of a nonarthritic population. These differences are likely to be due to the different age and gender distributions between an arthritic and nonarthritic population. Prevalence estimates, such as the ones reported here, are not conclusive evidence that OA increases the likelihood of developing CVD risk factors or CVD. If anything, they provide further evidence that CVD and arthritis may represent separate end points of a similar pathological process.^{42,43} While the importance of CVD risk factor reduction in all people is obvious, these prevalence estimates demonstrate that from a practical clinical perspective, modifiable CVD risk factors need to be aggressively managed in the arthritic population. It is important to be aware of the higher prevalence of CVD risk factors in the arthritic population when selecting from the many treatment options available today.

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Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis

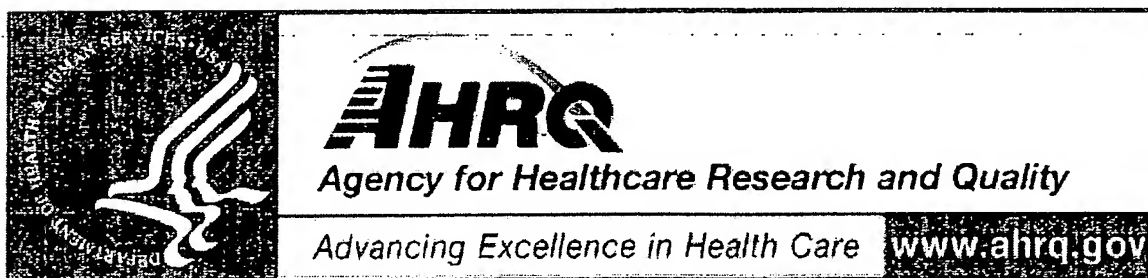
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This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Comparative Effectiveness and Safety of Analgesics for Osteoarthritis



Comparative Effectiveness Review

Number 4

**Comparative Effectiveness and Safety of Analgesics
for Osteoarthritis**

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0024

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**AHRQ Publication No. 06-EHC009-EF
September 2006**

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation:

Chou R, Helfand M, Peterson K, Dana T, Roberts C. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024.) Rockville, MD: Agency for Healthcare Research and Quality. September 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Acknowledgments

We would like to acknowledge with appreciation the members of the Technical Expert Panel for their advice and consultation. In addition, we would also like to acknowledge Eric Johnson, Ph.D., for reviewing this manuscript.

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Executive Summary

Background

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life. About 6 percent of U.S. adults aged 30 years or older have symptomatic osteoarthritis of the knee, and 3 percent have symptomatic osteoarthritis of the hip. Osteoarthritis increases with age: the incidence and prevalence increase two- to tenfold from age 30 to 65 and continue to increase after age 65. The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product, with more than half of these costs related to work loss.

Common oral medications for osteoarthritis include nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. Patients with osteoarthritis also use over-the-counter supplements not regulated by the U.S. Food and Drug Administration (FDA) as pharmaceuticals, including glucosamine and chondroitin, as well as topical agents. Opioid medications are also used for selected patients with refractory, chronic pain but are not recommended for first-line treatment of osteoarthritis and therefore not included in this review. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may vary for individual drugs within a class. Nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise) also help improve pain and functional status in patients with osteoarthritis.

A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the fewest serious adverse effects. NSAIDs decrease pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-1 protects the lining of the stomach from acid. COX-2 is found in joint and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis, low back pain, minor injuries, and soft tissue rheumatism. However, NSAIDs that also block the COX-1 enzyme (also called “nonselective NSAIDs”) can cause gastrointestinal bleeding. In the United States, there are an estimated 16,500 annual deaths due to NSAID-induced gastrointestinal complications, a higher death rate than that for cervical cancer or malignant melanoma. Theoretically, NSAIDs that block only the COX-2 enzyme (also called “coxibs,” “COX-2 selective NSAIDs,” or “selective NSAIDs”) should be safer with regard to gastrointestinal bleeding, but they also appear to be associated with increased rates of serious cardiovascular and other adverse effects. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain.

For this report, we defined the terms “selective NSAIDs” or “COX-2 selective NSAIDs” as drugs in the “coxib” class (celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib). We defined “partially selective NSAIDs” as other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam). Aspirin differs from other NSAIDs because it irreversibly inhibits platelet aggregation, and the salicylic acid derivatives (aspirin and salsalate)

were considered a separate subgroup. We defined “nonaspirin, nonselective NSAIDs” or simply “nonselective NSAIDs” as “all other NSAIDs.”

This report summarizes the available evidence comparing the benefits and harms of analgesics in the treatment of osteoarthritis.

Oral agents include:

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| • Aspirin | • Ketorolac |
| • Acetaminophen | • Lumiracoxib ¹ |
| • Celecoxib | • Meclofenamate sodium |
| • Choline magnesium trisalicylate ¹ | • Mefenamic acid |
| • Chondroitin | • Meloxicam |
| • Diclofenac | • Nabumetone |
| • Diflunisal | • Naproxen |
| • Etodolac | • Oxaprozin |
| • Etoricoxib ¹ | • Piroxicam |
| • Fenoprofen | • Rofecoxib ¹ |
| • Flurbiprofen | • Salsalate |
| • Glucosamine | • Sulindac |
| • Ibuprofen | • Tenoxicam ¹ |
| • Indomethacin | • Tiaprofenic acid ¹ |
| • Ketoprofen | • Tolmetin |
| • Ketoprofen ER | • Valdecoxib ¹ |

¹ These drugs are currently not approved by the FDA for use in the United States (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) or have been withdrawn from the market (rofecoxib and valdecoxib).

Questions addressed in this report are:

1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: The only benefits considered under this question are improvements in osteoarthritis symptoms from long-term use. Evidence of harms associated with NSAID use include long-term studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.*
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?
 - Demographic subgroups include age, sex, and race.
 - Coexisting diseases include hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous bleeding due to NSAIDs.

- Concomitant medication use includes anticoagulants.
3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?
 4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen, and salicylate.

A summary of the findings is shown in Table A.

Conclusions

Oral NSAIDs

Benefits: improvements in osteoarthritis symptoms

- **Nonselective NSAID vs. another nonselective NSAID**
 - Many trials found no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac) in efficacy for pain relief or improvement in function.
 - In one short-term trial, salsalate and aspirin did not differ significantly in efficacy for pain relief or symptom improvement.
 - No studies evaluated the comparative efficacy of salsalate or aspirin vs. a nonaspirin NSAID.
- **COX-2 selective (NSAID) vs. nonselective NSAID**
 - COX-2 selective NSAIDs and nonselective NSAIDs did not clearly differ in efficacy for pain relief, based on many good-quality, published trials.
- **COX-2 selective NSAID vs. different COX-2 selective NSAID**
 - Celecoxib and rofecoxib did not differ significantly in efficacy for pain relief at commonly used and comparable doses, based on consistent evidence from six good-quality trials.
 - No studies compared efficacy of COX-2s other than celecoxib and rofecoxib.

Harms: gastrointestinal (GI) and cardiovascular (CV)

- **Rofecoxib vs. nonselective NSAID**

- In the only large, long-term trial (VIGOR), rofecoxib 50 mg daily caused fewer serious ulcer complications than naproxen 1,000 mg daily in patients with rheumatoid arthritis but also significantly increased the risk of myocardial infarction. The overall rate of serious adverse events was higher with rofecoxib than with naproxen.
 - There were about 16 fewer symptomatic ulcers, including 5.2 fewer serious GI complications, for every 1,000 patients treated with rofecoxib vs. naproxen after a median of 9 months of treatment.
 - There were 3.0 additional myocardial infarctions for every 1,000 patients treated with rofecoxib compared to naproxen in VIGOR.
- Rofecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of randomized controlled trials (RCTs).
 - About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with rofecoxib compared to placebo in the systematic review.
- Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks.
- **Celecoxib vs. nonselective NSAID or placebo**
 - It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months. In the only large, published trial (CLASS), celecoxib at 800 mg daily did not decrease predefined serious ulcer complications overall compared with diclofenac and ibuprofen; the risk of serious GI events was lower than with ibuprofen, but not diclofenac, at 6 months in patients who did not use aspirin; and there was no reduction in serious GI events at the end of followup. The overall rate of serious adverse events with celecoxib was similar to the rate with ibuprofen and diclofenac.
 - In fair-quality meta-analyses of arthritis trials, most of which evaluated short-term use, celecoxib caused fewer ulcer complications than nonselective NSAIDs and did not increase the risk of myocardial infarction.
 - Celecoxib 400 mg twice daily was associated with an increased risk of serious CV events (CV death or myocardial infarction) relative to placebo in a long-term trial of polyp prevention.
 - Celecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of RCTs. Most of the

CV events with celecoxib were reported in two large polyp-prevention trials evaluating 200 mg or 400 mg twice daily, or 800 mg once daily.

- About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with celecoxib compared to placebo.

- **Valdecoxib vs. nonselective NSAID or placebo**

- Valdecoxib was associated with a lower risk of upper GI complications compared with diclofenac, ibuprofen, or naproxen in two fair-quality meta-analyses of published and unpublished trials.
- There have been too few events reported in RCTs of patients with chronic conditions to accurately assess CV risk associated with valdecoxib.
- Two short-term trials in a high-risk post-coronary-artery-surgery setting found that valdecoxib was associated with a two- to threefold higher risk of CV events compared with placebo.
- Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk.

- **Etoricoxib vs. nonselective NSAID**

- Etoricoxib was associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs in a fair-quality meta-analysis of 10 trials.
- In primarily short-term trials, systematic reviews of RCTs suggest that etoricoxib has a similar CV safety profile compared to other NSAIDs, with the possible exception of naproxen. Definitive conclusions are not possible because of small numbers of CV events.

- **Lumiracoxib vs. nonselective NSAID**

- Results from one large trial (TARGET) found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen.
- There was no statistically significant difference in rates of serious CV events between lumiracoxib relative to naproxen or ibuprofen in TARGET.
- Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib.

- **Partially selective NSAID vs. nonselective NSAID**

- Meloxicam: There were no significant differences in risks of serious GI events in several meta-analyses of up to 28 primarily short-term clinical trials, and no difference in CV risk in three observational studies.
- Nabumetone or etodolac: There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety.
- **Nonselective NSAID vs. nonselective NSAID or any COX-2 selective NSAID**
 - No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.
 - The CV safety of naproxen was moderately superior to that of any COX-2 selective NSAID in a large systematic review of RCTs.
 - There were 3.3 additional myocardial infarctions for every 1,000 patients treated with any COX-2 inhibitor instead of naproxen for 1 year.
 - The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs in a large systematic review.
 - In indirect analyses, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo.
- **Aspirin**
 - Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds compared to placebo or nonuse when given in long-term prophylactic doses.
 - There is insufficient evidence to assess the balance of GI and CV safety of higher dose aspirin as used for pain relief compared with nonaspirin NSAIDs.
- **Salsalate**
 - Salsalate was associated with a lower risk of adverse events than other selective and nonselective NSAIDs using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs.
 - Almost no data are available on CV safety.

Harms: mortality

- Individual trials were not large enough to detect differences in mortality between the

included drugs.

- One meta-analysis of celecoxib found no difference between celecoxib and nonselective NSAIDs, but there were few events.
- In one fair-quality cohort study, nabumetone was associated with a lower risk of all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.

Harms: hypertension, congestive heart failure (CHF), edema, and impaired renal function

- All NSAIDs and COX-2 inhibitors can cause or aggravate these conditions.
- There is good evidence from short-term trials that, on average, nonselective NSAIDs raise mean blood pressure by about 5.0 mm Hg (95-percent confidence interval [CI] 1.2 to 8.7). However, similar average blood pressure changes may not necessarily correspond with similar likelihoods of an event requiring withdrawal, medication change, or other clinical consequences.
- Evidence from good-quality observational studies suggests that rofecoxib is associated with greater risks of hypertension, CHF, and edema than celecoxib. Indirect evidence from various meta-analyses of either rofecoxib or celecoxib vs. nonselective NSAIDs are consistent with these findings. Direct randomized trial evidence, however, is limited in quantity and difficult to interpret because of possible non-equivalent dosing of drugs. Evidence regarding the comparative risk of renal dysfunction for celecoxib and rofecoxib is sparse.
- There was weak evidence that aspirin and sulindac have less hypertensive effect than other nonselective NSAIDs.
- There were no clear differences among other selective or nonselective NSAIDs for these adverse events.

Harms: hepatotoxicity

- Clinically significant hepatotoxicity was rare.
- Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo (1 additional case for every 53 patients treated with diclofenac).

Tolerability

- Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs were better or similarly tolerated and aspirin was less well tolerated.
- There were no clear differences in tolerability among COX-2 selective or

nonselective NSAIDs.

- Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs. Available evidence is somewhat sparse and mixed, with two of three short-term trials suggesting salsalate is less well tolerated than nonselective NSAIDs and older, flawed observational studies suggesting that salsalate is less toxic than nonselective NSAIDs.

Other oral agents: benefits and harms

• Acetaminophen

- Acetaminophen was modestly inferior to NSAIDs for pain and function in four systematic reviews.
 - Pain severity ratings averaged less than 10 points higher for acetaminophen compared to NSAIDs on 100-point visual analog scales.
- Compared with NSAIDs, acetaminophen had fewer GI side effects (clinical trials data) and serious GI complications (observational studies).
- Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies).
- One good-quality, prospective observational study found an increased risk of CV events with heavy use of acetaminophen that was similar to the risk associated with heavy use of NSAIDs.
- Acetaminophen at therapeutic doses does not appear to be associated with an increased risk of hepatotoxicity compared to nonuse in patients without underlying liver disease.

• Glucosamine and chondroitin

- In one large, good-quality trial the combination of pharmaceutical-grade glucosamine hydrochloride plus chondroitin (not currently available in the United States) was not superior to placebo among all patients studied. Neither glucosamine nor chondroitin alone was superior to placebo. In an analysis of a small subgroup of patients with at least moderate baseline pain, there was a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis.
- Systematic reviews of older trials found glucosamine modestly superior to oral NSAIDs and placebo in most trials, but there was some inconsistency between trials, most trials had some flaws, and results may not be directly applicable to the United States because the positive trials primarily evaluated pharmaceutical-grade glucosamine available in Europe.

- Only 2 of 20 placebo-controlled trials assessed effects of glucosamine on radiologic disease progression. One fair- and one good-quality trial found pharmaceutical-grade glucosamine superior to placebo for progression of knee joint space narrowing over 3 years.
- Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.

Effect of dosage and duration of treatment on the benefits and harms of oral medication use

- We found no studies evaluating the GI or CV safety of alternative dosing strategies (such as alternate day dosing, once daily versus twice daily dosing, or periodic drug holidays).
- The risk of GI bleeding increases with higher doses of nonselective NSAIDs.
- The most comprehensive systematic review of RCTs found no clear association between duration of exposure and CV risk of COX-2 inhibitors. However, estimates of CV risk with shorter duration of exposure are imprecise due to low numbers of events.
- The most comprehensive systematic review of RCTs found higher doses of celecoxib associated with increased CV risk, but could not determine the effects of dose on CV risk associated with rofecoxib due to low numbers of events at lower doses. Most trials of nonselective NSAIDs involved high doses.

Differences in demographic and clinical subgroups

- GI and CV complication rates are higher among older patients and those with predisposing comorbid conditions, but there is no evidence that the relative safety of different NSAIDs varies according to baseline risk.
 - Compared to nonuse of NSAIDs, one additional death per 1 year of use occurred for every 13 patients treated with rofecoxib, 14 with celecoxib, 45 with ibuprofen, and 24 with diclofenac in one large, population-based observational study of high-risk patients with acute myocardial infarction.
- There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse.
- Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of recurrent ulcer bleeding are high (around 5 percent after 6 months) in patients prescribed celecoxib or a nonselective NSAID plus a PPI.

Concomitant anticoagulant use

- Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to sixfold compared to anticoagulants alone.
- Reliable conclusions about the safety of selective NSAIDs used with anticoagulants are not possible due to flaws in existing observational studies, although there are case reports of serious bleeding events, primarily in the elderly.

Concomitant aspirin use

- In the CLASS studies, there was no difference in rates of ulcer complications between celecoxib and nonselective NSAIDs in the subgroup of patients who took aspirin.
- Concomitant low-dose aspirin use increased the rate of endoscopic ulcers by about 6 percent in both patients on celecoxib and those on nonselective NSAIDs in one meta-analysis.
- Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers (16-17 percent), which were significantly higher than those for placebo (6 percent) or aspirin alone (7 percent).
- The most comprehensive systematic review of RCTs found that compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs.

Effects of coprescribing H2-antagonists, misoprostol, or PPIs

- Consistent evidence from good-quality systematic reviews and numerous clinical trials found coprescribing of PPIs to be associated with the lowest rates of endoscopically detected duodenal ulcers relative to gastroprotective agents.
- Coprescribing of misoprostol is associated with similar rates of endoscopically detected gastric ulcers as coprescribing of PPIs.
- While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.
- The risk of endoscopic duodenal ulcers for *standard*-dose H2 blockers was lower than placebo, similar to misoprostol, and higher than omeprazole. Standard dosages of H2 blockers were associated with no reduction of risk for gastric ulcers relative to placebo.
- *Double (full)* dose H2 blockers were associated with a lower risk of endoscopic gastric and duodenal ulcers relative to placebo. It is unknown how full-dose H2 blockers compare to other antiulcer medications because head-to-head trials are lacking.

Comparison of oral medications with topical preparations

- **Topical NSAIDs: efficacy**
 - Studies of topical NSAIDs typically evaluated proprietary formulations not approved by the FDA.
 - Topical NSAIDs were similar to oral NSAIDs for pain relief in trials primarily of patients with osteoarthritis of the knee, with topical diclofenac (often with dimethyl sulphoxide [DMSO], a drug not approved for use in humans in the United States) best studied.
 - Topical ibuprofen was superior to placebo in several trials.
- **Topical NSAIDs: safety**
 - Consistent evidence from good-quality trials, systematic reviews, and observational studies found topical NSAIDs to be associated with increased local adverse events compared with oral NSAIDs.
 - Total adverse events and withdrawal due to adverse events were similar.
 - Data from one good-quality trial found topical NSAIDs superior to oral NSAIDs for GI events, including severe events, and changes in hemoglobin.
- **Topical salicylates and capsaicin**
 - Topical salicylates were no better than placebo in higher quality placebo-controlled trials.
 - Compared to placebo, one additional patient achieved pain relief for every eight that used topical capsaicin in a good-quality meta-analysis, but capsaicin was associated with increased local adverse events and withdrawals due to adverse events.

Balance of evidence and harms

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. Each was also associated with gaps in the evidence necessary to determine the true balance of benefits vs. harms. The role of selective and nonselective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence vary, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others. This is not surprising, given the complex tradeoffs between the many benefits (pain relief, improved function,

improved tolerability, and others) and harms (CV, renal, GI, and others) involved.

Individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of an increase in CV risk, for example, could be an acceptable tradeoff for some patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation medications). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

Remaining Issues

- The CV safety of nonselective NSAIDs has not been well studied in large, long-term clinical trials. Naproxen, in particular, may be associated with fewer CV risks than other NSAIDs and should be investigated in long-term, appropriately powered trials.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall tradeoffs between benefits and harms.
- The CV risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to continue to assess the effects of dose and duration as more data become available; current estimates of risks at lower doses and with shorter duration of exposure are less precise than estimates at higher doses and longer duration of exposure because of small numbers of events.
- Large, long-term trials of the GI and CV safety associated with full-dose aspirin, salsalate, or acetaminophen compared with nonaspirin NSAIDs or placebo are lacking. Recent observational data suggesting an increased CV risk with heavy use of acetaminophen highlight the need for long-term, appropriately powered clinical trials.
- Given the large number of patients who meet criteria for aspirin prophylaxis for CV events, more trials evaluating the dose-related effects of aspirin 50-1500 mg on GI benefits and CV safety are needed.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing

of certain COX-2 inhibitors could reduce CV risk, this hypothesis has not yet been tested in a clinical trial.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical-grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations of glucosamine and chondroitin with oral NSAIDs are needed, as these are likely to remain available even if the FDA approves pharmaceutical-grade formulations.
- No topical NSAIDs are FDA approved in the United States, yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO, which is not approved in the United States for use in humans. Cohort studies using large observational databases may be required to adequately assess CV risk.

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into this report, but found their results generally consistent with our conclusions:

- A fair-quality meta-analysis of arrhythmia and renal event (peripheral edema, hypertension, or renal dysfunction) risk from 114 randomized trials of COX-2 selective NSAIDs found rofecoxib associated with increased risks of arrhythmia (primarily ventricular fibrillation, cardiac arrest, or sudden cardiac death) and renal dysfunction (peripheral edema, hypertension, or renal dysfunction) relative to control treatments (placebo, other NSAIDs, or mixed/other). The increased risk was equivalent to approximately 1.1 additional arrhythmia events per 1,000 patients treated with rofecoxib. Celecoxib was associated with lower risks of renal dysfunction and hypertension than control treatments, although there was no difference for the pre-specified, primary composite renal outcome of peripheral edema, hypertension, renal dysfunction or arrhythmia. There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and either arrhythmia or renal events (no arrhythmia events reported with lumiracoxib).
- A good-quality meta-analysis of cardiovascular risk (primarily myocardial infarction) from 23 observational studies was largely consistent with our qualitative assessment of the observational literature. It found rofecoxib associated with a dose-dependent, increased risk of cardiovascular events that was detectable during the first month of treatment. Of the other NSAIDs, diclofenac was associated with the highest risk, followed by indomethacin and meloxicam. Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. Assessments of increased risk were modest (relative risks all <2.0), and all of the main analyses were associated with substantial between-study heterogeneity.

Table A. Summary of Findings on Comparative Effectiveness and Safety of Analgesics for Osteoarthritis, with Strength of Evidence

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
COX-2 selective NSAIDs	<ul style="list-style-type: none"> Good evidence COX-2-selective NSAIDs are comparable in efficacy (pain relief) to nonselective NSAIDs. Good evidence COX-2 selective NSAIDs are comparable in efficacy to each other. 	<ul style="list-style-type: none"> GI: Fair to good evidence of fewer serious GI events with COX-2 selective NSAIDs compared to nonselective NSAIDs, at least in the first 6 months of treatment. CV: Comparative data on CV risks of COX-2 selective vs. nonselective and partially selective NSAIDs are sparse, with a few exceptions (see below). Fair evidence that COX-2 selective NSAIDs are associated with increased risks of serious CV events (primarily myocardial infarction) compared to placebo. CV risks may increase with greater dosages and durations of treatment, but estimates of risks at lower doses and with shorter durations of treatment are imprecise due to small numbers of events. <ul style="list-style-type: none"> Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks. Cautions about CV risk apply primarily to rofecoxib and celecoxib, as CV safety data are less precise (due to small numbers of events) for valdecoxib, etoricoxib, and lumiracoxib. Other <ul style="list-style-type: none"> Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk. Fair evidence suggests that rofecoxib is associated with greater risk of hypertension, CHF, edema, and cardiorenal events than celecoxib. 	<ul style="list-style-type: none"> Good evidence that risk of GI bleeding and CV events increases with age. Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities.
NSAIDs : nonselective (including naproxen), partially selective	<ul style="list-style-type: none"> Good evidence nonselective and partially selective NSAIDs are comparable in efficacy to each other. 	<ul style="list-style-type: none"> GI: Good evidence that all nonselective NSAIDs are associated with comparable, dose-dependent increases in risk of serious GI events compared to none. Good evidence that coprescription of misoprostol or PPIs can attenuate this risk, but misoprostol is less well tolerated. <ul style="list-style-type: none"> No clear evidence (fair for meloxicam and poor for etodolac and nabumetone) that partially selective NSAIDs are associated with decreased risk relative to nonselective NSAIDs. CV: Data on CV risks of nonselective and partially selective NSAIDs are sparse, with a few exceptions: <ul style="list-style-type: none"> Fair evidence that high doses of ibuprofen and diclofenac carry similar risks of serious CV events compared to COX-2 selective NSAIDs. Fair evidence that naproxen is associated with a lower risk of CV events than COX-2 selective NSAIDs and no excess risk compared to placebo. Other: Fair evidence that diclofenac is associated with higher rates of aminotransferase elevations than other NSAIDs. 	<ul style="list-style-type: none"> Good evidence that risk of GI bleeding and CV events increases with age. Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities. Fair evidence that using NSAIDs concomitantly with anticoagulants increases GI bleeding risk three- to sixfold.

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Aspirin/ salsalate	<ul style="list-style-type: none"> No evidence comparing efficacy of aspirin or salsalate to COX-2s or NSAIDs. 	<ul style="list-style-type: none"> Good evidence that aspirin 50-1500 mg (for thrombotic event prophylaxis) is associated with greater risks of serious GI events compared to placebo or when added to warfarin. Good evidence that low-dose aspirin is effective for preventing CV events. Insufficient evidence to assess GI and CV risks associated with higher doses of aspirin for pain control or with salsalate. 	<ul style="list-style-type: none"> Good evidence that concomitant use of aspirin attenuates or eliminates the GI benefits of COX-2 selective NSAIDs. Fair evidence that concomitant use of low-dose aspirin does not eliminate CV risks when added to NSAIDs.
Acetaminophen	<ul style="list-style-type: none"> Good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs. 	<ul style="list-style-type: none"> Good evidence of lower risk of GI complications with acetaminophen compared to NSAIDs. Fair evidence of increased risk of blood pressure and renal dysfunction with acetaminophen compared to nonuse. Poor evidence (a single observational study) that heavy use of acetaminophen carries a similar CV risk compared to heavy use of NSAIDs. 	None
Glucosamine (pharmaceutical grade)/ chondroitin	<ul style="list-style-type: none"> Fair evidence (some inconsistency between clinical trials) that pharmaceutical-grade glucosamine and chondroitin are not more effective than placebo in unselected patients, including one recent, large, good-quality trial finding no beneficial effects from glucosamine or chondroitin alone or in combination. In an analysis of a small subgroup of patients with at least moderate baseline pain in the latter trial, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. Fair evidence of no clear difference in efficacy between pharmaceutical-grade glucosamine or chondroitin and NSAIDs. No studies compared glucosamine or chondroitin to acetaminophen. 	<ul style="list-style-type: none"> Good evidence that glucosamine and chondroitin are well tolerated and do not appear to be associated with serious adverse events. 	None

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Topical NSAIDs	<ul style="list-style-type: none"> Good evidence they are comparable to oral NSAIDs for pain relief in trials primarily of patients with knee osteoarthritis. Most trials of topical NSAIDs evaluate proprietary formulations not available in the United States. 	<ul style="list-style-type: none"> Good evidence that topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Good evidence that topical and oral NSAIDs are comparable in rates of total adverse events and withdrawals due to adverse events. Good evidence that topical NSAIDs are associated with fewer GI events, including severe events, and changes in hemoglobin compared to oral NSAIDs. 	None
Topical salicylates and capsaicin	<ul style="list-style-type: none"> Fair evidence that capsaicin, but not topical salicylates are superior for pain relief compared to placebo. 	<ul style="list-style-type: none"> Good evidence that topical capsaicin is associated with increased local adverse events and withdrawals due to adverse events compared to placebo. 	None

Abbreviations: CHF = congestive heart failure; COX = cyclo-oxygenase; CV = cardiovascular; GI = gastrointestinal; NSAID=nonsteroidal antiinflammatory drug; PPI=proton pump inhibitor.

Chapter 1. Introduction

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.² Among U.S. adults aged 30 or older, approximately 6% have symptomatic osteoarthritis of the knee, and 3% have symptomatic osteoarthritis of the hip.³ Osteoarthritis increases with age, with the incidence and prevalence increasing 2- to 10-fold from age 30 to 65, and continues to increase after age 65.⁴ Osteoarthritis accounts for more disability in walking, stair climbing, and other tasks requiring use of the lower extremities than any other disease, particularly in the elderly.⁵ The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product,³ with more than half of these costs related to work loss.⁵

In addition to non-pharmacologic interventions (such as physical therapy, weight reduction, and exercise), numerous medications and over-the-counter supplements are available to treat pain and potentially improve functional status in patients with osteoarthritis. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs within a class. Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Appendix A). Many are available at lower over-the-counter and higher prescription doses. Commonly used supplements sold over-the-counter and not regulated as pharmaceuticals by the FDA include glucosamine and chondroitin. Topical agents frequently used by patients with osteoarthritis are rubefacients (including capsaicin), NSAIDs, and other miscellaneous preparations.⁶ Opioid medications are also used for patients with chronic pain, especially if it is refractory to other therapies, but are not recommended for first-line treatment for osteoarthritis or other conditions because of risks of addiction, tolerance, diversion, and other adverse events.^{7,8}

NSAIDs exert analgesic, anti-inflammatory, and anti-pyretic effects by blocking *cyclo-oxygenases* (COX), enzymes that are needed to produce *prostaglandins*. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-2, found in joint and muscle, contributes to pain and inflammation. Because they block COX-2, non-steroidal anti-inflammatory drugs reduce pain compared to placebo in patients with arthritis,⁹ low back pain,¹⁰ minor injuries, and soft tissue rheumatism. Less is known about COX-3, which has been found in the cerebral cortex and cardiac tissue and appears to have effects on centrally-mediated pain.¹

NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the 1990s in the United States, nonaspirin NSAIDs are estimated cause 32,000 hospitalizations and 3,200 deaths annually from GI bleeding.¹¹ A risk analysis¹² based on a retrospective case-control survey of emergency admissions for upper GI disease in two United Kingdom general hospitals provided useful estimates of the frequency of serious GI complications from NSAIDs.¹³ In people taking NSAIDs, the 1-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647 (Table 1). In addition to age, prednisone use, disability level, and previous NSAID-induced GI symptoms are risk factors for GI bleeding.

Table 1. One year risk of GI bleeding due to NSAID

Age range (years)	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
<i>Risk in any one year is 1 in:</i>		
16-45	2100	12,353
45-64	646	3800
65-74	570	3353
> 75	110	647
Data are from Blower, ¹³ recalculated in Moore ¹² and in Bandolier ¹⁴		

NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. Theoretically, an NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. Appendix B¹⁵ summarizes the NSAIDs and their selectivity based on assay studies (done in the laboratory instead of in living patients). The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results, and assay method may not reliably predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs.

In addition to their propensity to cause GI bleeding, NSAIDs are also associated with adverse effects on blood pressure, renal function, and fluid retention. Mechanisms may involve attenuation of prostaglandin-mediated vasodilation, promotion of sodium and water retention, increased vascular resistance, and increased renal endothelin-1 synthesis.¹⁶⁻¹⁸

An association between selective COX-2 inhibitors and increased rates of myocardial infarction was first observed in the large, pivotal Vioxx Gastrointestinal Outcomes Research (VIGOR) trial comparing high-dose rofecoxib (50 mg) to naproxen 1000 mg.¹⁹ Reasons for the increase in thromboembolic cardiovascular event risk are complex and not completely understood, but may be related in part to suppression of endothelial-derived prostaglandin I₂ formation by selective COX-2 inhibition, in the setting of unaffected platelet production of prothrombotic COX-1 mediated thromboxane A₂.²⁰ Blood pressure elevations associated with COX-2 inhibitors may also play a role in increasing cardiovascular risk.²¹ On September 30, 2004, rofecoxib was withdrawn from the market after a long-term polyp prevention trial found an increased risk of myocardial infarction compared with placebo.²² On December 9, 2004, the US Food and Drug Administration issued a black-box warning for valdecoxib for life-threatening skin reactions and increased cardiovascular risk. This drug was subsequently also withdrawn voluntarily by the manufacturer.²³

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, anti-pyretic, and anti-inflammatory effects.²⁴ It is thought to be the most consumed medicinal drug in the world. Like the non-aspirin NSAIDs, aspirin's effects are due to blockade of cyclo-oxygenases. However, an important distinction between aspirin and non-aspirin NSAIDs is that aspirin also induces irreversible functional defects in platelets (although non-aspirin NSAIDs also have effects on platelet aggregation, they are short-lived). Because of these antiplatelet effects, low-dose aspirin is also used prophylactically to reduce the risk of thrombotic events.²⁵ However, even at doses of 325 mg daily or lower, the potential cardiovascular benefits must be balanced against dose-dependent risk of aspirin-induced adverse GI events. Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. However, salsalate is considered a relatively weak inhibitor of cyclo-oxygenases.²⁶

Acetaminophen (also known as paracetamol) is an anti-pyretic and analgesic medication that

is not thought to have significant anti-inflammatory properties. Although its mechanism of inducing analgesia is still not completely understood, it is thought to work in part by indirectly decreasing production of prostaglandins through inhibitory effects involving COX-2.^{16, 27} Acetaminophen is frequently recommended as a first line agent for osteoarthritis and other pain conditions because of its perceived favorable safety profile—particularly with regard to ulcer risk.²⁸

Chondroitin sulfate and glucosamine sulfate are natural compounds found in cartilage. Both are marketed to patients who have osteoarthritis. The precise mechanisms of action are unknown, but may involve promoting maintenance and repair of cartilage. Glucosamine, for example, has been shown to increase proteoglycan synthesis.²⁹ In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the U.S., by contrast, glucosamine and chondroitin are considered dietary supplements and are not regulated as pharmaceuticals. Adequate standardization of glucosamine and chondroitin preparations is a significant concern. It has been shown that the actual content often varies substantially from what is stated on the label.³⁰ Such inconsistencies may have implications on estimates of efficacy and safety for different commercial preparations.

Topical administration of NSAIDs could theoretically result in local analgesic and anti-inflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.³¹ Experimental studies indicate that topical administration is associated with substantially higher concentrations of NSAIDs in soft tissue (particularly meniscus and cartilage) and lower peak plasma concentrations compared with oral administration.⁶ For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and anti-inflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.³¹ Superior *in vivo* permeability characteristics, however, may not predict clinical effectiveness.

In contrast to topical NSAIDs, whose mechanism of action involves inhibition of cyclooxygenase, topical rubefacients are thought to relieve pain through counter irritation.^{6, 32} Although the mechanism of action of topical preparations containing salicylate esters is unclear, they are now usually classified as rubefacients rather than topical NSAIDs because they may not work via inhibition of cyclo-oxygenase.^{6, 33} Capsaicin, which is also often classified as a rubefacient, is derived from the hot chili pepper (*Capsicum* species). It is applied topically and thought to work by stimulating the release of substance P and other neuropeptides from sensory nerve endings.³⁴ Although this release can initially lead to burning and pain, analgesia occurs after repeated and continued application, as substance P becomes depleted. Although a wide variety of other rubefacients are available, only topical salicylates and capsaicin were included in this review.

The purpose of this report was to assess the comparative efficacy and safety of non-opioid oral medications (selective and non-selective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Scope and Key Questions

1. What are the comparative benefits and harms of treating osteoarthritis

with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: This question addresses the therapeutic benefits of long-term use for the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including use for other labeled indications such as the treatment of rheumatoid arthritis.)*

Oral NSAIDs include:

- | | |
|-----------------------------------|------------------------|
| • aspirin | • meclofenamate sodium |
| • celecoxib | • mefenamic acid |
| • choline magnesium trisalicylate | • meloxicam |
| • diclofenac | • nabumetone |
| • diflunisal | • naproxen |
| • etodolac | • oxaprozin |
| • etoricoxib* | • piroxicam |
| • fenoprofen | • rofecoxib* |
| • flurbiprofen | • salsalate |
| • ibuprofen | • sulindac |
| • indomethacin | • tenoxicam* |
| • ketoprofen | • tiaprofenic acid* |
| • ketoprofen ER | • tolmetin |
| • ketorolac | • valdecoxib* |
| • lumiracoxib* | |

* These drugs are currently not approved (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) for use in the United States by the FDA or have been withdrawn from the market (rofecoxib and valdecoxib)

Other oral agents include acetaminophen, chondroitin, and glucosamine. See Appendix A for a detailed listing of pharmacokinetics, indications, and recommended dosing information for all included drugs. Appendix C shows low, medium and high doses for the more commonly used NSAIDs.

For this report, we defined the terms “selective NSAID” or “COX-2 selective NSAID” as drugs in the “coxib” class (e.g. celecoxib, rofecoxib, and valdecoxib). We grouped etodolac, nabumetone, and meloxicam into a separate category that we referred to as “partially selective NSAIDs,” to explore how in vitro differences in COX-2 selectivity might translate into clinical differences in safety. The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined “non-aspirin, non-selective NSAIDs” or simply “non-selective NSAIDs” as all other NSAIDs. We included evidence on the efficacy and safety of the COX-2 inhibitor rofecoxib, even though it is no longer available in the U.S., because it was the first drug to be associated with cardiovascular risks and therefore provides important historical context and illustrates important issues to consider when evaluating the risks and benefits of selective and non-selective NSAIDs. For other COX-2 inhibitors not approved by the FDA for use in the U.S.

(lumiracoxib and etoricoxib) or withdrawn from the market (valdecoxib), we focused only on evidence regarding long-term, serious GI and CV adverse events, which is likely to be the most important factor driving future decisions regarding their use.

“Benefits” include relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales.³⁵

Visual analogue scale (VAS): Using VAS, patients indicate their level of pain, function, or other outcome by marking a scale labeled with numbers (such as 0 to 100) or descriptions (such as “none” to “worst pain I’ve ever had”). An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient’s subjective experience of pain. This poses a challenge in objectively comparing different patients’ scores, or even different scores from the same patient.

Categorical pain scales consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose among categories that may not accurately describe their pain. A variety of disease-specific and non-specific scales are used to assess these outcomes in patients with osteoarthritis. Commonly used categorical pain scales include:

- The *Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*, a 24-item, disease-specific questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.³⁶
- The *Medical Outcomes Short Form-36 (SF-36)* health survey, a commonly used general instrument for measuring health-related quality of life across different diseases.³⁷
- *Patient Global Assessment of Disease Status* and *Investigator Global Assessment of Disease Status*. The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or categorical scale.
- *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.

Another method for measuring outcomes is classifying patients dichotomously as “responders” or “non-responders.” Responders are often defined as patients with at least a 50% improvement in pain or function. The *Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria*, for example, were developed through a consensus process and classifies patients as responders if they meet specific pre-defined criteria ($\geq 50\%$ improvement in pain or function that was ≥ 20 mm on a 100 mm VAS, or a $\geq 20\%$ improvement in at least two of pain, function, or patient global assessment that was ≥ 10 mm on a 100 mm VAS).³⁸

“Harms” include tolerability (not having to stop the drug due to adverse effects); cardiovascular, hepato-, renal, and gastrointestinal toxicity; and increased risk for hospitalizations, drug interactions, and death. For gastrointestinal toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric

outlet obstruction, though we also evaluated other gastrointestinal side effects (such as nausea, dyspepsia, and gastrointestinal tolerability). We only considered rates of endoscopic ulcers when data on clinical ulcer complications were incomplete or not available.

2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?

- Demographic subgroups include age, sex, and race.
- Co-existing diseases include hypertension, edema, ischemic heart disease, heart failure, PUD, and history of previous bleeding due to NSAIDs.
- Concomitant medication use includes anticoagulants and aspirin.

3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors?

4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?

Topical preparations include:

- Capsaicin
- Diclofenac
- Ibuprofen
- Ketoprofen
- other NSAIDs
- salicylates

Chapter 2. Methods

Topic Development

The topic for this report was nominated in a public process. The key questions were developed by investigators from the Oregon EPC with input from a Technical Expert Panel (TEP) formed for this project. Contacted via teleconference, the TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. Results from previously conducted meta-analyses and systematic reviews on these topics were sought and used where appropriate and updated when necessary. To identify systematic reviews, in addition to MEDLINE, we searched the Cochrane Database of Systematic Reviews and the websites of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Bandyolier, and the NHA Health Technology Assessment Programme.

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews (through 3rd Quarter 2005) the Cochrane Central Register of Controlled Trials (through 3rd Quarter 2005) and Ovid @MEDLINE (1966- July, 2005.) We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis (see Appendix D for the complete search strategy). Other sources include reference lists of review articles and unpublished materials from the US Food and Drug Administration (FDA). Pharmaceutical manufacturers were invited to submit scientific information packets, including citations if applicable. All 2,665 citations from these sources were imported into an electronic database (EndNote® 9.0) and considered for inclusion.

Study Selection

Systematic reviews and controlled trials pertinent to the key questions were included. We retrieved any blinded or open, parallel or crossover randomized controlled trial that compared one included drug to another, another active comparator, or placebo. We also included cohort and case-control studies with at least 1,000 cases or participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.

Data Extraction

The following data were extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), method of outcome ascertainment if available, and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if available.

Quality Assessment

Assessing Research Quality

We assessed the internal validity (quality) of systematic reviews and randomized trials based on the predefined criteria listed in Appendix E. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).³⁹ We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix E) assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, reported adequate detail of included studies, and used appropriate methods to synthesize the evidence. We included systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we considered this a methodological shortcoming.

For assessing the internal validity of observational studies, we evaluated whether they used nonbiased selection methods; whether rates of loss to follow-up were acceptable; whether pre-defined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal quality rating methods.⁴⁰ We therefore did not use a formal scoring system to rate the quality of the observational studies included in this review, but noted methodological deficiencies in any of the above areas when present.

Assessing Research Applicability

The applicability of trials and other studies was assessed based on whether the publication

adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the sponsor.

Rating a Body of Evidence

Overall quality ratings for an individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

We assessed the overall strength of evidence for a body of literature about a particular key question, by examining the type, number and quality of studies; the strength of association; the consistency of results within and between study designs; and the possibility for publication bias. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered “good-quality.”) For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

Data Synthesis

Effectiveness Versus Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes of most importance to patients, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of successful treatment, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales. Further discussion of these issues is available at <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

Data Presentation

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. We also performed two quantitative analyses for this review. An important limitation of observational studies of NSAIDs is that none simultaneously assessed the risk for

serious cardiac and GI events. We therefore re-analyzed data from a set of observational studies that reported rates of three different serious adverse events in the same population. We assumed that the adverse events occurred independently and that the logarithm of the rate ratios was distributed normally. After estimating the effect (number of events prevented or caused) for each of the three adverse events, we estimated the net effects on all three serious adverse events using Monte Carlo simulation.

We also pooled clinical success rates and withdrawal due to adverse events from head-to-head trials of topical versus oral NSAIDs using a random effects model (Dersimonian-Laird method, using RevMan® statistical software). We performed standard chi-square tests for heterogeneity. Because only four trials were available for pooling, we did not attempt meta-regression analyses to evaluate potential sources of heterogeneity.

Chapter 3. Results

Overview

Searches identified 2,789 publications: 1,522 from the Cochrane Central Register of Controlled Trials, 68 from the Cochrane Database of Systematic Reviews, 1015 from MEDLINE and 184 from the combination of other sources listed above. There were also 59 studies not previously reviewed for inclusion that were suggested through peer review or public comment or published after the searches were conducted. Following application of inclusion criteria, 351 publications were included in this review.

Key Question 1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

Benefits: Effectiveness and Efficacy

Effectiveness Studies

No controlled clinical trials of COX-2 inhibitors and/or NSAIDs met all major criteria for an effectiveness study (conducted in mainly primary care or office-based settings, used broad enrollment criteria, and evaluated longer-term, “real-life” outcomes).

Efficacy

Non-selective NSAIDs vs. other NSAIDs. Several good-quality systematic reviews by the Cochrane Collaboration evaluated trials that compared non-aspirin NSAIDs for OA of the hip (trials published through 1994),⁴¹ for OA of the back (through 1998),¹⁰ and for OA of the knee (through 1997).⁴² These reviews found no clear differences among non-aspirin and primarily non-selective NSAIDs in efficacy. There were also no differences between diclofenac and sustained-release etodolac in patients with OA of the knee⁴³ or between piroxicam and standard formulation etodolac in patients with OA of the knee or hip⁴⁴ in two trials published subsequent to the Cochrane reviews.

Nabumetone was similar in efficacy to the non-selective NSAIDs diclofenac SR⁴⁵ and etodolac⁴⁶ in two 4-week trials, as reported in the Cochrane review of OA of the knee.⁴²

No studies of meloxicam, salsalate, or aspirin were included in any Cochrane reviews. We identified nine double-blinded trials of meloxicam 7.5 mg, 15 mg, and 25 mg versus other NSAIDs and found no clear or consistent differences in efficacy.⁴⁷⁻⁵⁵ In two of the trials, however, patients taking non-selective NSAIDs were significantly less likely to withdraw due to

lack of efficacy than patients taking meloxicam.^{49, 54}

In the only head-to-head trial of salsalate (3 g) in patients with OA, efficacy was similar to that of 3.6 g soluble aspirin after two weeks of treatment.⁵⁶

Celecoxib vs. non-selective NSAIDs. Celecoxib and non-selective NSAIDs were associated with similar decreases in symptom severity and improvements in functional capacity (PGA, WOMAC) after 6- to 24-weeks in five published trials of patients with primarily OA.⁵⁷⁻⁶⁰

A good-quality systematic review funded by the makers of celecoxib reached similar conclusions based on data from published and unpublished trials of at least 12 weeks' duration in patients with either OA or RA.⁶¹

Using an alternative endpoint, a more recent systematic review (published in 2005) with access to all unpublished manufacturer-held clinical trial reports reached slightly different conclusions about the relative efficacy of celecoxib and NSAIDs.⁶² Moore et al meta-analyzed data from 31 primarily short-term (≤ 12 weeks) trials and concluded that celecoxib at dose of 200-400 mg was associated with slightly higher rates of withdrawals due to lack of efficacy compared to non-selective NSAIDs (RR 1.1; 95% CI 1.02, 1.23). CLASS remains the pivotal, long-term study (6 to 13 months) of celecoxib in patients with rheumatoid and osteoarthritis. It randomized a total of 7,968 patients to celecoxib or the non-selective NSAIDs ibuprofen or diclofenac. A higher proportion of non-selective NSAID patients withdrew due to lack of efficacy (14.8% vs. 12.6%, $p=0.005$). However, CLASS focused on assessment of adverse events rather than efficacy, and other efficacy results were reported. SUCCESS-1, a shorter (12-week), double-blind, randomized trial of 13,274 patients with osteoarthritis, found no clinically meaningful differences between celecoxib 100 mg or 200 mg twice daily and the non-selective NSAIDs diclofenac or naproxen.⁶³

Rofecoxib vs. non-selective NSAIDs. We were unable to determine whether all manufacturer-sponsored trials of rofecoxib versus NSAIDs have been published.^{19, 64-76} All but one of the trials included osteoarthritis patients, and all but two^{70, 72} were supported by the manufacturer of rofecoxib. All but two of the OA trials^{73, 76} have been previously analyzed in a good-quality Cochrane review.⁷⁷ Conclusions of the Cochrane review are consistent with our findings that there were no consistent differences between rofecoxib and non-selective NSAIDs in efficacy for OA. In addition, a pivotal, good-quality trial (VIGOR) and a good-quality Cochrane review found rofecoxib equivalent to naproxen in efficacy for rheumatoid arthritis.^{19, 78}

Valdecoxib vs. non-selective NSAIDs. In clinical trials submitted to the FDA, valdecoxib was as effective as ibuprofen (800 mg 3 times/day), diclofenac (75 mg twice daily), and naproxen (500 mg twice daily) in treating osteoarthritis symptoms. Published trials found no difference in efficacy between valdecoxib and naproxen⁷⁹⁻⁸¹ or ibuprofen or diclofenac.⁸² A fifth trial found no difference in efficacy between valdecoxib 20-40 mg and slow-release diclofenac 75 mg in treating rheumatoid arthritis.⁸³

Comparisons between selective COX-2 inhibitors. We found six published randomized, multicenter, fair-to-good quality trials that directly compared COX-2 inhibitors for osteoarthritis of the knee.⁸⁴⁻⁸⁹ Pharmaceutical manufacturers were reported as funding sources in all but one study.⁸⁸ This small (N=30), short-term (7 days), fair-quality trial found that rofecoxib 25 mg and celecoxib 200 mg had similar effects on patients' pain intensity, 3-hour pain relief, global

assessment of efficacy and rescue medication use.⁸⁸ Two trials of higher-risk osteoarthritic patients with hypertension (both funded by the maker of celecoxib) found no differences in efficacy between rofecoxib 25 mg and celecoxib 200 mg daily, but reported a higher rate of adverse events with rofecoxib.^{84, 85}

The remaining three trials appeared to enroll patients with similar demographics and baseline levels of pain and were more homogeneous in design (see table below).^{86, 87, 89} All compared rofecoxib 25 mg qd and celecoxib 200 mg qd in patients with flare-ups of chronic osteoarthritis of the knee and were 6 weeks in duration. One trial, funded by the manufacturer of celecoxib, found no difference in efficacy between rofecoxib and celecoxib, but a higher rate of adverse events with rofecoxib.⁸⁶ Another (VACT, or *Vioxx Acetaminophen Celecoxib Trial*)⁸⁷ trial, funded by the manufacturer of rofecoxib, found rofecoxib more effective than celecoxib, with no differences in rates of adverse effects. The most recent study, funded by the maker of celecoxib,⁸⁹ found no difference in either efficacy or adverse effects between celecoxib and rofecoxib.

Table 2. Comparison of rofecoxib and celecoxib in flare-ups of chronic osteoarthritis of the knee

Characteristic	McKenna ⁸⁶	Geba ⁸⁷	Gibofsky ⁸⁹
Rofecoxib 25mg (n)	59	95	190
Celecoxib 200mg (n)	60	97	189
Aspirin 325 qd permitted	Yes	No	Yes
Mean age	62	62.6	62.9
Mean osteoarthritis duration	10.5 years	10 years	9 years
Percent white	80%	85%	NR
Baseline pain on walking (score)	72	72	68
Discontinued trial by 6 wks:			
Rofecoxib 25mg	16%	19%	15%
Celecoxib 200mg	22%	17%	16%

All three trials were probably adequately randomized and blinded, and didn't have statistically significant differences in baseline characteristics. Gibofsky and colleagues hypothesized that neither McKenna nor Geba were powered sufficiently to measure differences between celecoxib and rofecoxib. Gibofsky viewed the McKenna study as being powered only to compare active treatments with placebo and the Geba study as powered to compare rofecoxib with acetaminophen. Therefore, Gibofsky, and colleagues set out to conduct a study powered to compare celecoxib and rofecoxib, with a sample size based on results of the McKenna study.

Efficacy results are summarized in Table 3 below. Mean changes in WOMAC VAS score for Walking Pain were similar for celecoxib 200 mg and rofecoxib 25 mg across trials. In the Geba trial, rofecoxib was associated with significantly greater mean reductions than celecoxib on VAS scores for WOMAC Rest Pain and Night Pain and a similar mean reduction in Morning Stiffness. WOMAC Composite Score results from Geba and Gibofsky were conflicting. In the Gibofsky trial, there were no differences, but in the Geba trial, there were significant differences favoring rofecoxib for mean changes in the WOMAC pain (7 points) and stiffness (8 points) subscales. However, an analysis of data from randomized trials estimated that the minimal perceptible improvement for each WOMAC scale was a difference of 11 mm.⁹⁰

Table 3. Head to head efficacy comparisons at 6 weeks (mean change from baseline)

	WOMAC VAS Scores					WOMAC Composite Subscales			
	Walking pain	Rest pain	Morning stiffness	Night pain	Arthritis pain	Pain	Stiffness	Function	Total
Geba ⁸⁷									
Rofecoxib	-42	-31.1*	-36.2	-32.7**	nr	-35.4*	-35*	-29.7	-26
Celecoxib	-36.2	-23.4	-29.1	-22.6	nr	-28.6	-27.9	-24.9	-26
McKenna ⁸⁶									
Rofecoxib	-38	nr	nr	nr	-40	nr	nr	nr	nr
Celecoxib	-38	nr	nr	nr	-39	nr	nr	nr	nr
Gibofsky ⁸⁹									
Rofecoxib	-29.2	nr	nr	nr	nr	-42.6	-34.7	-35.5	-20.1
Celecoxib	-31.5	nr	nr	nr	nr	-42.0	-36.7	-37.9	-22.1

*p≤0.05; **p<0.001; nr=not reported

Safety: Serious Gastrointestinal and Cardiovascular Events

Rofecoxib and Celecoxib: GI and CV Safety in CLASS and VIGOR

GI Safety

Two pivotal studies were large enough to evaluate serious complications of peptic ulcer disease (bleeding, perforations, obstruction) as a primary endpoint in average-risk patients (those without a recent UGI bleed). The VIGOR trial¹⁹ evaluated rofecoxib versus naproxen and the CLASS trials⁶⁰ evaluated celecoxib versus ibuprofen and diclofenac.

VIGOR (Vioxx Gastrointestinal Outcomes Research) Trial. VIGOR, a randomized, double-blind trial, compared twice the highest recommended dose of rofecoxib (50 mg daily) to naproxen 500 mg twice a day in 8,076 patients with rheumatoid arthritis. VIGOR found a statistically significant reduction in complicated upper GI events (defined as perforation, obstruction, or severe upper gastrointestinal bleeding. During a median follow-up of 9 months, the rates of confirmed upper gastrointestinal events were 3.0% vs. 1.4% (NNT to prevent one event 62), and the rates of complicated, confirmed upper gastrointestinal events were 0.9% vs. 0.4% (NNT 192).

VIGOR met all but one of the criteria for a good-quality study. The one weakness was the varying duration of exposure among study participants. The duration of VIGOR was designed to be both time and event driven, so that the trial would terminate after a minimum of 120 patients experienced clinical upper GI events (or 40 patients experienced complicated upper GI events) and for at least 6 months after randomization of the last patient enrolled. Because patients were enrolled over a 6-month period, patients in VIGOR were followed for varying lengths of time. The longest time a patient could have remained in the study was 13 months, but half of the patients were followed for 9 months or less, and only about 1,000 patients (13%) were followed for longer than 10 months. By 13 months, about 29% of the subjects had discontinued the study drugs. Similar proportions discontinued naproxen or rofecoxib because of an adverse event (naproxen—16.1%, rofecoxib—16.4%).

In 2003, the VIGOR investigators published a *post hoc* analysis of lower GI events, defined

as bleeding with a 2 g/dL drop in hemoglobin or hospitalization, or hospitalization for perforation, ulceration, diverticulitis, or obstruction.⁹¹ There were 11 events in the rofecoxib group and 24 events in the naproxen group (0.41 versus 0.89 per 100 patient-years; RR 0.46, 95% CI 0.22 to 0.93). The absolute risk difference (per 100 patient-years) was -0.48 (95% CI -0.91 to -0.05), with a NNT of 208. When the investigators combined the analysis of lower GI events with previously reported results on upper GI complications (0.6 with rofecoxib versus 1.4 with naproxen per 100 patient-years⁹²), the rates of all serious GI events were 0.96 for rofecoxib and 2.26 per 100 patient-years for naproxen (relative risk 0.43, 95% CI 0.27 to 0.67, NNT 77).

CLASS (Celecoxib Long-term Arthritis Safety Study.) CLASS was designed as two trials with separate patient recruitment and randomization procedures: one compared celecoxib 400 mg twice a day with ibuprofen 800 mg three times a day, and the other compared celecoxib 400 mg twice a day with diclofenac 75 mg twice a day.⁶⁰ Because the FDA was concerned that selective COX-2 inhibitors could interfere with the benefits of COX-2 in ulcer healing and lead to a long term increase in GI complications without warning symptoms, the pre-specified primary outcome was “ulcer-related complications.”⁹³ Another pre-specified outcome was ulcer related complications plus symptomatic ulcers. The planned maximum duration of the trials were 15 and 12 months, respectively, or until at least 20 ulcer-related complications occurred in each trial, or 45 in both trials combined.⁹⁴ The protocols stated that celecoxib would be claimed to be different from traditional NSAIDs only if there were statistically significant differences between celecoxib and each of the comparators, as well as between celecoxib versus the comparator groups combined.

The CLASS trials were stopped early after the predefined threshold of ulcer complications occurred. However, the analysis and reporting of the results as presented in the main publication in JAMA were in part incomplete and differed in some ways from the protocols. The JAMA article reported truncated 6-month results even though the median duration of follow-up was 9 months (range 6 to 13 months), and combined the ibuprofen and diclofenac results without reporting the results of the two trials separately.⁶⁰ Subsequently, additional details of the study have been made public on the FDA web site⁹⁴ and have been extensively analyzed. The findings of the FDA analysis suggest that the published results of CLASS are, in part, misleading because they appear to selectively report results at the point in time at which celecoxib was most effective.⁹⁵⁻⁹⁷

There were 3,987 subjects randomized to celecoxib and 3,981 subjects randomized to non-selective NSAIDs in the CLASS trials. For the combined outcome of ulcer complications or symptomatic ulcers, the JAMA article reported that patients on celecoxib experienced fewer GI complications compared with patients in the combined NSAID groups (32/3987 versus 51/3981, annualized incidence rates 2.08% vs. 3.54%, $p=0.02$),⁶⁰ while the rate of complicated ulcers alone was not significantly different (13/3987 vs. 22/3981, annualized incidence rates 0.76% vs. 1.45%, $p=0.09$). However, by 12 months, according to FDA documents (see Table 14, FDA Medical Officer Review)⁹⁴ there was no longer a trend favoring celecoxib for the primary outcome of complicated ulcers. There were 17/3987 events in the celecoxib group (0.43%) versus 21/3981 (0.53%) in the NSAID groups combined.⁹⁴ This difference was not statistically significant (relative risk 1.10, 95% CI 0.47 to 2.58^{97,98}, also see Figure 4, Scheiman review⁹⁹). For the individual comparisons between celecoxib and ibuprofen or diclofenac, which were not reported in the JAMA article, there was no difference in the rate of ulcer complications at either 6 months or at the end of follow-up.⁹⁷ For the outcome of ulcer complications or symptomatic ulcers, celecoxib was superior to ibuprofen, but not to diclofenac at either 6 months or at the end

of follow-up.⁹⁷

Authors of CLASS have not completely explained the reasons for selective reporting of results, though they contend that combining the two trials and reporting ulcer complications plus symptomatic ulcers as a primary outcome were permitted by the protocols.^{100, 101} However, reporting only combined results appears to obscure differences between the results for the two comparator drugs.⁹⁶ The investigators' main argument for reporting truncated data is that results after 6 months were not interpretable because of high and differential rates of drop-outs due to symptomatic ulcers, which could have biased results against celecoxib because of depletion of high-risk patients in the non-selective NSAID arms.^{100, 101} On closer inspection, however, this rationale appears flawed, as neither symptomatic ulcers nor gastrointestinal symptoms predicted ulcer complications.⁹⁶ Furthermore, simply truncating data is not considered an acceptable method for resolving issues related to high drop-out rates.

Twenty per cent of the patients in the CLASS trial took aspirin in addition to their study drug. When patients taking aspirin were excluded from the analysis, there were fewer confirmed serious ulcer complications in the celecoxib group than in the ibuprofen group ($p=0.03$).^{94, 97} However, serious ulcer complications for celecoxib and diclofenac were equivalent even when patients taking aspirin were excluded from the analysis.

Changes in hemoglobin or hematocrit were not a primary outcome of CLASS and were not reported in the main JAMA publication. However, rates of significant hemoglobin (>2 g/dL) and/or hematocrit drops (≥ 0.10), a surrogate marker for GI blood loss, are available from the FDA Medical Officer Review.⁹⁴ Over the entire study period, patients randomized to celecoxib were significantly less likely to experience declines in these laboratory parameters (87/3701 or 2.4%) relative to patients randomized to either diclofenac (82/1849 or 4.4%) or ibuprofen (102/1802, 5.7%). Celecoxib was also superior when patients were stratified according to aspirin use (4.1% vs. 6.9% and 7.5%) or non-use (1.9% vs. 3.7% and 5.2%). However, the significance of these findings is unclear as they were not associated with differences in clinically relevant outcomes (such as rates of MI, angina, or congestive heart failure).

In summary, the CLASS trials did not demonstrate a statistically significant advantage over either diclofenac or ibuprofen for the primary endpoint of complicated ulcers for all patients enrolled over the full duration of follow-up. Celecoxib appeared superior to ibuprofen, but not diclofenac, in a subgroup of subjects not taking aspirin. In its decision regarding labeling for celecoxib, the FDA agreed with its Advisory Committee recommendations that CLASS did not demonstrate a safety advantage in upper gastrointestinal safety for celecoxib compared with either ibuprofen or diclofenac.¹⁰²

Comparison between VIGOR and CLASS. There are several possible reasons why rofecoxib (VIGOR), but not celecoxib (CLASS), significantly reduced ulcer complications. First, patient populations and study designs differed. VIGOR included patients aged 50 or older with rheumatoid arthritis, while CLASS had a broader age range of patients with either osteoarthritis or rheumatoid arthritis. VIGOR also prohibited the use of aspirin while CLASS did not. However, the rate of ulcers in the patients taking a control drug was almost three times as high in VIGOR as in CLASS, although rates of ulcer complications were similar. In addition, VIGOR compared rofecoxib to naproxen and CLASS compared celecoxib to diclofenac and ibuprofen. This could have affected the results if the non-selective comparator NSAIDs are associated with differential risk of ulcers. Finally, it is possible that rofecoxib, which has greater COX-2 selectivity, is truly more gastroprotective than celecoxib.

CV risk in VIGOR. Findings from the VIGOR trial raised concerns that the putative GI safety benefits of COX-2 selective NSAIDs relative to non-selective NSAIDs may have come at the expense of increased cardiovascular events. The main publication of VIGOR¹⁹ reported that “the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.” This corresponds to one additional heart attack for every 333 patients treated with rofecoxib instead of with naproxen. A re-analysis of VIGOR with three additional myocardial infarctions not included in the results originally submitted for journal publication estimated a relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen among all patients, and 3.00 (95% CI 0.91 to 12.78) among patients in whom aspirin was not indicated.¹⁰³ For patients who had indications for aspirin, 8 MIs occurred during 105 person-years of exposure to rofecoxib, compared with no MIs during 102 person-years of exposure to naproxen. Blinded adjudication of the VIGOR trial data classified 45/4047 (one in every 90) rofecoxib patients and 19/4029 (one in 212) naproxen patients as having serious thrombotic events (heart attack, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest, and sudden death).¹⁰⁴ This corresponds to one additional serious thrombotic event for every 156 patients taking rofecoxib.

CV risk in CLASS. The original publication of the CLASS trials, using 6-month data, reported that celecoxib had no effect on the rate of myocardial infarction or for any cardiovascular event (stroke, myocardial infarction, or angina) compared with diclofenac and ibuprofen.⁶⁰ The number of myocardial infarctions was 10/3987 (0.3%) with celecoxib versus 11/3981 (0.3%) with the non-selective NSAIDs). The full CLASS data on thrombotic events were analyzed in more detail by White and colleagues,¹⁰⁵ who also found no differences in the rates of any significant cardiovascular event for the overall sample or for the subgroup who did not use aspirin. For the overall sample, myocardial infarctions occurred in 19/3987 (0.5%) of patients on celecoxib and 13 (0.3%) on diclofenac or ibuprofen. In fact, more detail about the design of the CLASS trials is necessary to judge the validity and generalizability of these results. In particular, reporting of longer-term data is important because 6 months of exposure to celecoxib may not be enough time to assess cardiovascular risk. At 8 months in the VIGOR trial there was no significant difference between rofecoxib and naproxen in the cumulative incidence of events. From 8 to 12 months, differences in the incidence of myocardial infarction between rofecoxib and naproxen became apparent (Figure 1 of Mukherjee¹⁰⁶). This observation could be due to increased power due to a larger number of events with longer follow-up, or in part to a duration-dependent increase in risk. Based on the pattern observed in VIGOR, if celecoxib is associated with an increased risk of cardiovascular events, it may not be seen until 10 or 12 months of followup. In the VIGOR trial, 2,140 subjects, about one-fourth of the original sample, were available for 10 months of followup, and 1,045 were available for 12 months. In the CLASS trials, 2,770 subjects, about one-third of the original sample, had at least 9 months of follow-up, and 1,126 had at least 12 months of follow-up, suggesting that an analysis should have been able to detect an increased risk of cardiovascular events similar to that observed in VIGOR, if it was present (see Table 4, FDA Medical Officer Review⁹⁴).

White and colleagues argue that their meta-analysis shows that celecoxib is safer than rofecoxib.¹⁰⁵ To support their argument, they note that the annualized rate of all cardiovascular

thromboembolic events in the naproxen group in the VIGOR trial and the non-aspirin celecoxib users in the CLASS trial were similar. However, this comparison of rates across the VIGOR and CLASS studies is imprecise. After 8 months, about 0.4% of naproxen patients had experienced an event in VIGOR, compared to about 0.8% of non-aspirin celecoxib users in CLASS. It is not clear whether or not this is a statistically significant difference. By contrast, Mukherjee and colleagues suggested that the selective NSAIDs as a class might be associated with an increased risk of myocardial infarction because the 0.8% rate of myocardial infarction on celecoxib in the CLASS trials and the 0.74% rate on rofecoxib in VIGOR are both higher than the 0.52% rate observed in a meta-analysis¹⁰⁷ of patients receiving placebo in studies of aspirin prophylaxis.¹⁰⁶ In our opinion, all of these conclusions are unsubstantiated because they involve cross-trial and historical comparisons.

The importance of analyzing longer-term data and assessing dose effects are underscored by the results of the long-term Adenoma Prevention with Celecoxib (APC) trial in a different population—that of patients receiving celecoxib for colorectal polyp prevention.¹⁰⁸ This trial, which randomized patients to celecoxib versus placebo, was terminated after 33 months because of a higher rate of cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) in the celecoxib arms. According to Figure 1 in the main publication of this trial,¹⁰⁸ the difference in rates of events became most apparent only after twelve to eighteen months. There was also a non-significant increase in risk with higher compared to lower doses of celecoxib. Compared with placebo, the relative risk of cardiovascular events in patients randomized to celecoxib 400 mg twice daily was 3.4 (95% CI 1.4 to 8.3) compared to 2.5 (95% CI 1.0 to 6.3) in patients randomized to 200 mg twice daily.¹⁰⁸ Much of the increased risk was due to differences in rates of fatal or nonfatal myocardial infarctions, which occurred in 22/1356 (1.6%) of celecoxib users and 3/679 (0.4%) of patients on placebo.¹⁰⁹ On the other hand, data from PreSAP,¹¹⁰ another polyp prevention trial, and preliminary data from ADAPT,¹¹¹ an Alzheimer's prevention trial, found no significant increase in cardiovascular events with celecoxib 400 mg once daily (PreSAP, RR 1.3, 95% CI 0.6 to 2.6¹⁰⁹) or 200 mg twice daily (ADAPT) compared to placebo. However, the lack of an association could be due to insufficient power to detect a difference because of the small number of myocardial infarctions associated with celecoxib in these trials (2 in ADAPT¹¹² and 9 in PreSAP¹⁰⁹). Alternatively, the smaller relative risk in PreSAP relative to APC could be related to a higher placebo event rate in PreSAP (7.2 versus 3.4 per 1000 patient-years).¹⁰⁹ SUCCESS-I, a recently published, large (N=13,274) trial of osteoarthritis patients, also reported no significant difference in rates of cardiovascular thromboembolic events with celecoxib 100 mg or 200 mg twice daily versus diclofenac or naproxen (10 events or 0.55/100 patient-years in the combined celecoxib arms versus 1 event or 0.11/100 patient-years in the non-selective NSAID arms, $p=0.11$), but may have been too short in duration (12 weeks) and have recorded too few events to detect a difference.⁶³

Overall rate of serious adverse events in CLASS and VIGOR. One Canadian analysis used FDA materials to analyze the rates of serious adverse events, defined as death, hospitalization, or “any life-threatening event, or event leading to severe disability” in the CLASS and VIGOR trials.¹¹³ This measure combines the rates of serious upper GI complications (in which coxibs are expected to have an advantage over NSAIDs) with other serious adverse events. The numbers of all serious adverse events were drawn directly from FDA materials, pages 7 and 8 (rofecoxib¹¹⁴) and 57 (celecoxib⁹⁴).

In the Canadian re-analysis, shown in Table 4, the rates were calculated using the number of patients as the denominator. These simple rates are compared with the number of serious upper GI events, which constitute only about 10% of all serious adverse events (the two rightmost columns in the table). Using all serious adverse events as the criterion for “harm,” the number-needed-to-harm one person was 82 for celecoxib vs. diclofenac, 129 for celecoxib vs. ibuprofen, 100 for celecoxib vs. diclofenac and ibuprofen, and 65 for rofecoxib vs. naproxen. The Canadian authors also pooled the results for celecoxib and rofecoxib, assigning more weight to VIGOR, which had a longer duration than CLASS. In the pooled analysis, the number needed to harm was 78 for the selective COX-2 inhibitors versus non-selective NSAIDs and was statistically significant.

Table 4. Re-analysis of the CLASS and VIGOR Trials¹¹³

Trial	ALL SERIOUS ADVERSE EVENTS		SERIOUS UPPER GI EVENTS	
	Treatment	Control	Treatment	Control
CLASS ⁶⁰ (Celecoxib 400 mg)	270/3987 (6.8%)	230/3981 (5.8%)	20/3987 (0.5%)	24/3981 (0.6%)
VIGOR ¹⁹ (Rofecoxib 50 mg)	378/4047 (9.3%)*	315/4029 (7.8%)	16/4047 (0.4%)*	37/4029 (0.9%)

*statistically significant vs. control group.

For the VIGOR trial, the FDA calculated rates of serious adverse events in exactly the same manner as the Canadian investigators.¹¹⁴ The FDA analysis shows that the rates of each serious adverse event (except GI adverse events) were higher for rofecoxib than for naproxen. For the CLASS trials, the FDA used patient-years as the denominator instead of a simple proportion to calculate rates of serious adverse events.⁹⁴ This approach was used because the two trials that make up CLASS had different durations. In the FDA analysis, the rates of all serious adverse events combined were 11.6 per 100 patient-years for celecoxib; 10.3 per 100 patient-years for diclofenac, and 10.6 per 100 patient-years for ibuprofen, a difference that was not statistically significant.

In summary, the FDA data clearly show that these two coxibs, in doses higher than those commonly used in practice, do not reduce the overall rate of serious adverse events, and may have increased them. It should be noted, however, that not all serious adverse events are equal in importance to patients and physicians. A reduction in the rate of one kind of adverse event might be considered more important than an increase in another one.

Rofecoxib and Celecoxib: Further Analyses of CV Toxicity and GI Safety

The GI and CV risk profiles of celecoxib and rofecoxib relative to one another and to NSAIDs, placebo, or no treatment have also been assessed in numerous meta-analyses of randomized trials and observational studies. We were unable to obtain final results of one systematic review evaluating the GI safety associated with selective and non-selective NSAIDs in time to include it in this report.¹¹⁵ However, analyses of GI safety with celecoxib and rofecoxib in this systematic review were based on results from CLASS,⁶⁰ VIGOR,¹⁹ the then-unpublished SUCCESS-1 trial of celecoxib,¹¹⁶ and two previously published meta-analyses^{117, 118} (all included in this report).

Rofecoxib. VIGOR remains the only individual trial large enough to adequately assess rates of upper GI complications with rofecoxib and non-selective NSAIDs in patients with arthritis. However, the manufacturer of rofecoxib also sponsored a prospective meta-analysis of GI safety from eight smaller phase 2b/3 osteoarthritis trials (N=5425).¹¹⁸ It found the 12-month combined incidence of perforations, symptomatic ulcers, and upper GI bleeding significantly lower with rofecoxib compared to non-selective NSAIDs (1.3% vs. 1.8%, $P=0.046$; rate per 100 patient-years 1.33 vs. 2.60, RR 0.51, 95% CI 0.26 to 1.00). The rate of ulcer complications alone, however, was not reported. A Food and Drug administration review has been critical of several aspects of this meta-analysis.¹¹⁹ It notes that it is not clear how assiduously investigators of the trials adhered to the pre-specified protocols (for example, by not delivering the prespecified type of primary source material mandated in the original protocol), and that most (50 of 62) cases were unblinded before the adjudication process occurred. In addition, the FDA review suggests that simple pooling and comparisons of the rofecoxib and the non-selective NSAIDs outcomes may be misleading because study duration varied, different patient withdrawal criteria were applied, different diagnostic surveillance methods (including endoscopic surveillance in two trials) were employed, doses of rofecoxib varied, and different comparator NSAIDs were used. Rates of complicated ulcers at 12 weeks, for example, were substantially higher in patients on ibuprofen (1.12%) compared with diclofenac (0.19%). Further, combining symptomatic ulcers and ulcer complications may be less informative because the morbidity associated with ulcer complications is substantially higher than the morbidity associated with symptomatic ulcers. Data reported on the FDA web site (page 78) indicate that only six complicated ulcers in 3,357 patients on rofecoxib and five in 1,564 patients on non-selective NSAIDs (cumulative incidence at 12 months 0.45% vs. 0.55%) occurred; the difference was not statistically significant (relative risk using Cox proportional hazards model 0.51, 95% CI 0.16 to 1.69).¹¹⁹

An updated meta-analysis of 20 trials sponsored by the manufacturer of rofecoxib (excluding VIGOR) reported 0.21 vs. 0.45 confirmed complicated PUBs per 100 patient-years of exposure ($p=0.03$) among 10,026 subjects randomized to rofecoxib and 7,046 to non-selective NSAIDs. However, this meta-analysis was rated fair-quality because it did not evaluate the effects of study quality, duration of therapy, or dose (about 30% of patients received 12.5 mg of rofecoxib, about 50% received 25 mg, and about 10% received 50 mg).¹²⁰ With regard to duration of exposure, the results as presented in this study are somewhat misleading, as the rate of PUBs are reported as occurring over 24.8 months (last point in time at which there were >200 patients left in each treatment group), even though the median duration of exposure was only 3 months. Only one-quarter of the patients receiving rofecoxib had over 6 months of exposure.

The only randomized controlled trial evidence clearly demonstrating a lower risk of complicated ulcers with long-term use of rofecoxib compared with non-selective NSAIDs therefore comes from VIGOR, which evaluated a higher-than-conventional dose of 50 mg of rofecoxib. Although the most recent meta-analysis¹²⁰ reporting rates of complicated ulcers is consistent with VIGOR, its results appear primarily applicable to patients with shorter-term (<6 months) exposure to rofecoxib.

Celecoxib. One manufacturer-funded, fair-quality meta-analysis examined the endpoint of "UGI ulcer complications" in 14 RCTs of celecoxib (not including CLASS) versus placebo or non-selective NSAIDs (usually naproxen).¹²¹ The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The strength of this meta-analysis was that the endpoint—upper

GI bleeding with endoscopic findings of an ulcer or large erosion, perforation, or gastric outlet obstruction—was similar to those used in the VIGOR and CLASS trials. A Safety Committee adjudicated potential ulcer complications in a blinded manner. These endpoints were ascertained through a monitoring program that appears to have been superimposed on all of the trials; it is not clear how assiduously investigators complied with this program. Not all of the included trials have been published, and their quality was not assessed as part of the meta-analysis. In addition, like the meta-analysis of rofecoxib trials described above, results of the trials were simply pooled despite differences in dose of celecoxib, duration of therapy, or which comparator NSAID was used. In the 14 trials, there were 2 UGI ulcer complications among 6,376 patients in the celecoxib group (3 per 10,000), 9 among 2,768 in the NSAIDs group (33 per 10,000) and none in the placebo group (0/1,864). This corresponded to annual rates of two per 1,000 per year for celecoxib and about 17 per 1,000 per year for NSAIDs ($p=0.002$).

There are several possible reasons why the results of the meta-analysis differed from those of CLASS, which did not clearly show a decreased risk of UGI ulcer complications for celecoxib compared to diclofenac and ibuprofen. First, the incidence of serious ulcer complications in CLASS was much higher than in the trials included in the meta-analysis. In the CLASS trials, the annualized rate of serious ulcer complications was 7.6 per 1,000 per year for celecoxib and 14.5 per 1,000 per year for the two NSAIDs combined.⁶⁰ The nearly four-fold higher rate of ulcer complications in the CLASS trials compared to the other celecoxib trials could be due in part to enrollment of a higher-risk population, the use of concomitant medications, the dose of celecoxib evaluated, or other factors. In CLASS, for example, 21% of patients randomized to celecoxib were on aspirin and 30.6% on corticosteroids. By contrast, only 12.4% of patients in the meta-analysis were taking aspirin, and 13.5% were on corticosteroids.¹²¹ In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16.5% of celecoxib patients in the meta-analysis. Another potential explanatory factor is that the high dose of celecoxib used in CLASS—400 mg twice daily—was evaluated in only about 10% of the patients in the meta-analysis. It is possible that using higher doses of celecoxib could attenuate GI safety benefits because of incomplete COX-2 selectivity. Finally, different comparator NSAIDs could be associated with different risks of GI complications. In the meta-analysis, six trials ($N=6151$) compared celecoxib to naproxen versus only three trials ($N=2439$) that compared celecoxib to diclofenac or ibuprofen (the drugs evaluated in CLASS). Pooling data from trials evaluating different comparator NSAIDs could obscure differential effects on GI safety if they were present.

Moore, McQuay and others conducted a separate meta-analysis of celecoxib trials for osteoarthritis or rheumatoid arthritis, with funding from Pfizer and the Oxford Pain Relief Trust.⁶² The authors obtained a declaration from Pfizer that they had received information on all completed clinical trials of celecoxib and would be permitted to publish the results no matter what their findings showed. However, much of the data on which this meta-analysis was based remains inaccessible to the public. The unpublished data used in this meta-analysis add value in that they may help provide the most comprehensive and precise estimates of adverse events. However, although the meta-analysis methods appeared appropriate, it is impossible to verify whether the meta-analysis assessed validity appropriately, abstracted outcomes correctly, or otherwise confirm the reproducibility of the meta-analysis.

Moore and colleagues reviewed over 180,000 pages of company documents, which included detailed information on study methods. All 31 included trials were rated 5 out of 5 on the Jadad quality scale, and 16 out of 16 on an eight-item validity scale. Only two of the 31 trials were

longer than 12 weeks in duration. The meta-analysis found celecoxib associated with a lower risk of hemoglobin fall of 20 g/L or more (a marker for a significant GI bleed) (RR 0.72, 95% CI 0.56 to 0.92) and hematocrit fall of 5% or more (RR 0.78, 95% CI 0.69 to 0.89) compared with non-selective NSAIDs.⁶² Although the risk of complicated ulcers was not evaluated as a separate outcome, celecoxib was also associated with a lower risk of clinical ulcers and bleeds than non-selective NSAIDs in 18 trials (RR 0.61, 95% CI 0.46 to 0.81). When the analysis was limited to trials evaluating doses of 200 or 400 mg daily of celecoxib (in other words, excluding the results of CLASS), the benefit was more pronounced (RR 0.35, 95% CI 0.22 to 0.56).

The largest (N=13,274) randomized controlled trial (SUCCESS-1) of celecoxib (included in the Moore meta-analysis) assessed ulcer complications through 12 weeks.⁶³ It found that in patients with osteoarthritis, celecoxib was associated with a lower incidence of ulcer complications than naproxen or diclofenac (0.1% versus 0.8%, OR 7.02, 95% CI 1.46 to 33.8; p=0.008). Post hoc analysis indicated that non-aspirin users in the non-selective NSAID groups had a significantly higher risk of ulcer complications when compared to non-aspirin users in the celecoxib group (OR=12.05, 95% CI 1.45-100.09.) Among aspirin users, there was no statistically significant difference in the rates of ulcer complications for both NSAIDs and celecoxib.⁶³

Systematic Reviews and Meta-analyses of CV Toxicity

Rofecoxib. VIGOR and other randomized trials of rofecoxib have been extensively re-examined to further explore its cardiovascular risk profile. Many questions have been raised in response to the disparate findings of these analyses and a myriad of possible explanatory factors have been proposed.

Rofecoxib versus non-selective NSAIDs. In October 2001, a fair-quality meta-analysis published in *Circulation*¹²² by Konstam and colleagues reported pooled results from 23 rofecoxib Phase IIb through V trials sponsored by Merck. The investigators stratified results by patient group (rheumatoid arthritis, osteoarthritis, or Alzheimer's disease) and by control group (placebo, naproxen, or non-naproxen NSAID). The risk of cardiovascular events was 1.69 times higher for rofecoxib than for naproxen (95% CI 1.07 to 2.69), but was not elevated in trials comparing rofecoxib to non-naproxen NSAIDs (RR 0.79, 95% CI 0.40 to 1.55) (Table 5). The authors hypothesized that rofecoxib might have been an "innocent bystander" in the VIGOR trial. In other words, rather than rofecoxib increasing the rate of cardiovascular events, naproxen might have reduced it.

A problem with the Konstam analysis¹²² is that the non-naproxen and naproxen studies are not directly comparable. VIGOR, the only long-term COX-2 trial to demonstrate a significant reduction in serious GI events, used rofecoxib 50 mg, prohibited aspirin, and followed patients for 9 months. By contrast, some of the non-naproxen-controlled studies were 12 weeks or shorter in duration, permitted aspirin, or used lower doses of rofecoxib. The data presented in the meta-analysis are also inadequate to judge the quality of the included studies and how concomitant aspirin use, duration of treatment, or dose might have affected rates of cardiovascular events, as adjustment using individual patient risk factors was not performed.

A subsequent meta-analysis by Reicen and colleagues, also rated fair-quality, provided a more detailed analysis of eight phase IIb/III trials of osteoarthritis patients previously included in the Konstam analysis.¹²³ Although the Konstam meta-analysis cites a planned duration of follow-up of 86 weeks for these trials, the Reicen meta-analysis reports that the mean duration of

treatment was actually 3½ months. Like the Konstam study, insufficient information was provided to judge the quality of the studies analyzed or the effects of concomitant aspirin. The incidence of thrombotic cardiovascular adverse events was lower in the rofecoxib treatment group (1.93/100 patient-years) compared with the non-naproxen NSAID (ibuprofen, diclofenac, or nabumetone) groups (2.27/100 patient-years) (Table 5).

The conclusion of the Reicen analysis—that there were no significant differences between rofecoxib and non-naproxen NSAIDs—may be valid for this set of studies. However, the results do not address the more specific question of whether rofecoxib is safe at the dosage proven to reduce serious GI events associated with long-term use. The analysis combined data from all rofecoxib doses (12.5, 25, and 50 mg/day); only 545 of the patients received the 50 mg/day dose. Although 50 mg/day is higher than doses used conventionally, the issue of dose may be important because only the 50 mg dose has been shown to reduce serious GI adverse events compared to non-selective NSAIDs in a long-term trial.¹⁹ It is possible that lower doses of rofecoxib do not increase cardiovascular events compared with non-naproxen NSAIDs. However, even though lower, conventional doses of rofecoxib would be expected to be associated with lower long-term rates of GI ulcer complications compared to higher doses, this has not been proven in clinical trials.

Using a different methodology from the studies by Konstam and Reicen, a good-quality meta-analysis funded by the Swiss National Science Foundation came to different conclusions (Table 5).¹²⁴ Juni and colleagues included 18 randomized controlled trials of rofecoxib in patients with chronic musculoskeletal disorders (N=25,273), using published data on myocardial infarction as well as unpublished data available from the FDA. They found that the risk of myocardial infarction was higher in patients in the rofecoxib arms of trials compared with patients in the combined comparator arms (naproxen, non-naproxen NSAIDs, or placebo) (RR 2.24, 95% CI 1.24 to 4.02). The risk did not vary according to dose of rofecoxib or duration of therapy (shorter versus longer than 6 months). Trials with an external endpoint committee had a substantially higher risk for myocardial infarction (RR 3.88, 95% CI 1.88 to 8.02) than those without an external endpoint committee (RR 0.79, 95% CI 0.29 to 2.13). VIGOR contributed 8,076 of the 21,432 included in the meta-analysis. However, even when the results of VIGOR were excluded, the increased risk of myocardial infarction in trials with an external endpoint committee persisted (RR 2.5, 95% CI 1.1 to 6.0).¹²⁵

Table 5. CV events in trials of rofecoxib versus non-selective NSAIDs: meta-analyses

Study	Outcome	Comparison	Relative risk (95% CI)
Konstam, 2001 ¹²²	Cardiovascular events	Rofecoxib versus non-naproxen NSAIDs	0.79 (0.40-1.55)
		Rofecoxib versus naproxen	1.69 (1.07-2.69)
Reicin, 2002 ¹²³	Cardiovascular events	Rofecoxib versus non-selective NSAIDs	1.44 (0.65-3.17)
Juni, 2004 ¹²⁴	Myocardial infarction	Rofecoxib versus any comparator	2.24 (1.24-4.02)
		Subgroup analyses:	
		Rofecoxib versus non-naproxen NSAIDs	1.55 (0.55-4.36)
		Rofecoxib versus naproxen	2.93 (1.36-6.33)

Unlike the previous meta-analyses by Reicen and Konstam, the Juni meta-analysis analyzed aggregated study-level data, evaluated the effects of variables related to methodologic quality (allocation concealment and use of an external endpoint committee), and assessed the outcome of myocardial infarction (rather than composite cardiovascular endpoints, which could have diluted the effects on myocardial infarction rates). A major point of contention, however, centers on

whether the Juni meta-analysis inappropriately combined results from different control interventions. Although Reicin and others have criticized this method of analysis because different control interventions may be associated with different risks for myocardial infarction,¹²⁶ Juni and colleagues' methods appear defensible based on their meta-regression analyses for potential sources of heterogeneity. They found that the only significant source of variation between study results was related to the use of an independent, external endpoint committee, and not to the type of control intervention. For studies with an external endpoint committee, the relative risks for myocardial infarction for rofecoxib compared with placebo, non-naproxen NSAIDs, or naproxen were 2.31, 2.98, and 3.72, respectively, with overlapping confidence intervals ($p=0.41$ for interaction).¹²⁵ The Reicin and Konstam meta-analyses did not assess the effects of this potential source of bias. Other criticisms of Juni have centered on its exclusion of two Alzheimer's trials (discussed below) and on some of its statistical methods (such as adding 0.5 to both arms of a trial when no events occurred in one of the arms). However, Juni and colleagues appeared to follow pre-specified inclusion criteria (trials of patients with musculoskeletal disease), and the statistical methods for dealing with empty cells meet current standards for conducting meta-analysis.¹²⁷ A post-hoc re-analysis of the Juni study sponsored by the manufacturer of rofecoxib and criticizing its methods and conclusions is available on-line, but has not been published in the peer-reviewed literature.¹²⁸

A fourth, fair-quality meta-analysis evaluated the cardiovascular risks of selective versus non-selective NSAIDs.¹²⁹ However, it only reported results for all COX-2 inhibitors pooled together. It is discussed in the section on cardiovascular risks associated with non-selective NSAIDs.

Rofecoxib versus placebo. The manufacturer-funded meta-analyses by Konstam and Reicin found no significant differences in cardiovascular risk between rofecoxib and placebo.^{122, 123} In the Konstam analysis, the relative risk of cardiovascular events (cardiovascular, hemorrhagic, or unknown death; nonfatal myocardial infarction; and nonfatal stroke) was 0.85 (95% CI 0.51 to 1.38).¹²² A total of 33 cardiovascular events were reported in the rofecoxib arms. In the Reicin analysis, the incidence of thrombotic cardiovascular AEs was 2.71/100 patient-years in the rofecoxib group and 2.57/100 patient-years in the placebo group (7 events reported in the rofecoxib arms).¹²³ There were too few events to evaluate the risk of myocardial infarction alone: 3 in the rofecoxib arms in one meta-analysis¹²³ and 19 fatal and nonfatal myocardial infarctions or resuscitated cardiac arrests in the other.¹²² In the Juni meta-analysis, the relative risk for myocardial infarction with rofecoxib relative to placebo was 1.04 (95% CI 0.34 to 3.12) when all trials were pooled, but 2.31 (95% CI 0.49 to 10.82) in trials with an external endpoint committee.¹²⁵

In two subsequent trials of cognitively impaired adults, rates of thrombotic vascular events were similar for rofecoxib 25 mg and placebo.^{130, 131} Four thrombotic vascular events (myocardial infarction not reported separately) occurred in 321 patients randomized to rofecoxib (1.2%) compared to 11 of 327 (3.4%) randomized to placebo in one 12-month trial of 692 patients (mean age=75.5 years) with mild to moderate Alzheimer's dementia.¹³⁰ In the second trial, 38 of 723 patients with mild cognitive impairment randomized to rofecoxib (5.2%) and 36 of 728 randomized to placebo (4.9%) had a confirmed serious thrombotic vascular event after 115-130 weeks (mean age=74.9 years); the number of confirmed nonfatal myocardial infarctions was 13 versus 10.¹³¹ However, more deaths occurred in the rofecoxib group in this trial (24 or 3.3% versus 15 or 2.1%).

On the other hand, in another long-term (the Adenomatous Polyp Prevention on Vioxx, or APPROVe) trial of a different population—that of patients receiving rofecoxib for prevention of colon polyps—rofecoxib 25 mg/day was associated with an increased risk of cardiac events (myocardial infarction, sudden death from cardiac causes, or unstable angina pectoris) relative to placebo (RR 2.80, 95% CI 1.44 to 5.45).¹³² Though the rate of events appeared to diverge only after 18 months in the initially published report,¹³² a subsequent analysis that included adverse events originally censored because they occurred more than 14 days after discontinuation of therapy suggests that the curves began to diverge by 4 to 6 months.¹³³ The risk of cerebrovascular events and peripheral vascular events were not significantly higher on rofecoxib (RR 2.32, 95% CI 0.89 to 6.74 and 0.46, 95% CI 0.08 to 2.03, respectively). Reasons for the discordant findings between the APPROVe and the Alzheimer's trials are unclear but could be related to differential underlying risk in the populations studied, duration of exposure, or differential use of aspirin or other antiplatelet agents.

The most recent and comprehensive meta-analysis included 37 placebo-controlled trials of rofecoxib.¹²⁹ It includes data from the trials evaluated in the earlier meta-analyses¹²²⁻¹²⁴ as well as newer information from the long-term polyp prevention and cognitive impairment trials. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. The meta-analysis was rated fair quality because it did not adequately assess the quality of included trials. Rofecoxib was associated with greater risks relative to placebo for the outcomes “any vascular event” (1.5% or 98/6638 versus 1.1% or 72/6415, RR 1.38, 95% CI 1.01 to 1.87) and myocardial infarction (0.8% or 54/6638 versus 0.5% or 30/6415, RR 1.76, 95% CI 1.14 to 2.73), but not for the outcomes stroke or vascular death. This is equivalent to approximately one additional myocardial infarction per 289 patients exposed to rofecoxib for one year instead of placebo. About 85% of the vascular events occurred in patients on a 25 mg dose of rofecoxib. Approximately 40% (21 of 54) of the myocardial infarctions were from the APPROVe trial.¹³²

Table 6. CV events in trials of rofecoxib versus placebo: meta-analyses

Study	Outcome	Number of events	Relative risk for (95% CI)
Konstam, 2001 ¹²²	Combined cardiovascular events	33	0.84 (0.51-1.38)
Reicin, 2002 ¹²³	Combined cardiovascular events	7	1.42 (0.24-6.22)
Juni, 2004 ¹²⁵	Myocardial infarction	Not reported	1.04 (0.34-3.12); all trials 2.31 (0.49 -10.82); only trials with external endpoint committee
Kearney, 2006 ¹²⁹	Myocardial infarction	54	1.76 (1.14-2.73)

Celecoxib. Five meta-analyses (three funded by the manufacturer of celecoxib^{62, 134, 135}) have analyzed the cardiovascular risks associated with celecoxib in primarily unpublished trials.^{62, 129, 134-136} The first, a fair-quality study by White and others, included 13 new drug application studies and two large post-marketing trials (CLASS and SUCCESS) of 18,942 patients randomized to celecoxib with osteoarthritis or rheumatoid arthritis.¹³⁴ Only two of the 15 trials were longer than 12 weeks in duration. The meta-analysis did not provide enough information about the design of the included studies to judge their quality. A total of 25 cardiovascular events (0.8%) and 6 myocardial infarctions (0.2%) occurred in patients randomized to celecoxib.

There were no differences in risk of cardiovascular events (cardiovascular, hemorrhagic and unknown deaths; nonfatal MI, or nonfatal stroke), fatal myocardial infarction, or nonfatal myocardial infarction between patients randomized to celecoxib versus those randomized to placebo, all NSAIDs, or naproxen (Table 7). There were also no differences in the subgroup of patients who were aspirin non-users. The authors did not perform an analysis of risk associated with different doses of celecoxib.

Table 7. CV events in trials of celecoxib: meta-analysis of 15 trials in patients with arthritis¹³⁴

Comparison	Relative risk for cardiovascular, hemorrhagic and unknown deaths; nonfatal MI; or nonfatal stroke (95% CI)
<i>All patients</i>	
Celecoxib versus placebo	0.85 (0.23 to 3.15)
Celecoxib versus all NSAIDs	1.06 (0.70 to 1.61)
Celecoxib versus naproxen	0.85 (0.29 to 2.46)
<i>Aspirin nonusers</i>	
Celecoxib versus placebo	0.60 (0.11 to 3.29)
Celecoxib versus all NSAIDs	0.86 (0.48 to 1.56)
Celecoxib versus naproxen	0.82 (0.18 to 3.70)

A second, more comprehensive meta-analysis was presented to the FDA's Arthritis Advisory Committee in February 2005.¹³⁵ It included 41 trials of celecoxib (N=24,933) for chronic conditions; 33 of the trials were in patients with osteoarthritis or rheumatoid arthritis. Only four of the 41 trials were longer than 12 weeks in duration. The investigators used full follow-up data from the CLASS trials (2,320 patient-years for 3,987 patients). In addition to the composite outcome of any cardiovascular thromboembolic event, the analysis also reported separate analyses for myocardial infarction, stroke, and peripheral vascular events. Over 80% of the cardiovascular events occurred in three large trials: CLASS (N=7,968), SUCCESS (N=13,194), and CAESAR (N=916) (the latter trial remains unpublished). The methods and limitations of this study were similar to the White meta-analysis. There were no significant differences between celecoxib and comparators for myocardial infarction, though event rates were low: only nine myocardial infarctions occurred among 7,462 celecoxib-exposed patients (0.12%) in the placebo-controlled trials. There were also no significant differences for any other cardiovascular thromboembolic event.

Table 8. CV events in trials of celecoxib: meta-analysis of 41 trials¹³⁵

Comparison	Relative risk for myocardial infarction (95% CI)
<i>All patients</i>	
Celecoxib ≥200 mg/day versus placebo	1.58 (0.92-2.72)
Celecoxib ≥200 mg/day versus non-selective NSAIDs	1.65 (0.38-7.21)
<i>Aspirin nonusers</i>	
Celecoxib ≥200 mg/day versus placebo	1.40 (0.61-3.21)
Celecoxib ≥200 mg/day versus non-selective NSAIDs	1.64 (0.17-15.33)

Another meta-analysis of manufacturer-held reports of 31 trials by Moore and colleagues found that celecoxib was not associated with a significantly increased risk for myocardial infarction compared with non-selective NSAIDs, any active comparator (including rofecoxib or

paracetamol), any comparator (including placebo), or any non-coxib comparator using a fixed-effect model in patients with rheumatoid or osteoarthritis, though trends towards increased risk were present (Table 9).⁶² The overall proportion of patients randomized to celecoxib with myocardial infarction was less than 0.3% (fewer than 60 cases in the largest comparison). There were too few myocardial infarctions in the celecoxib arms of trials comparing celecoxib to placebo (10 events), paracetamol (0 events), or rofecoxib (1 event) to analyze differences in risk. In the two largest trials included in the meta-analysis (CLASS and SUCCESS-I), myocardial infarctions occurred in 0.23% (29 of 12,787) of patients randomized to celecoxib 200 to 800 mg and in 0.18% (15 of 8,375) randomized to a non-selective NSAID (RR 1.7, 95% CI 0.88 to 3.2).

Although this study appears to adhere to high standards for conducting meta-analysis, its results are not verifiable because it analyzed publicly inaccessible data. In addition, myocardial infarctions in the included trials were as reported by investigators, and not subject to adjudication. The duration of exposure to celecoxib in the trials varied, with a mean of about 7 months. The authors of the meta-analysis were unable to perform an analysis on effects of duration of exposure, because the trial reports generally did not provide sufficient information on median duration of use.

Table 9. MI's in trials of celecoxib: meta-analysis of 31 trials in patients with arthritis⁶²

Comparison	Relative risk for myocardial infarction
Celecoxib 200 or 400 mg/day versus NSAID	1.9 (0.87 to 4.1)
Celecoxib any dose versus NSAID	1.6 (0.93 to 2.6)
Celecoxib any dose versus any active comparator	1.4 (0.87 to 2.3)
Celecoxib any dose versus any comparator	1.4 (0.88 to 2.2)
Celecoxib any dose versus non-coxib comparator	1.4 (0.88 to 2.2)

A fourth meta-analysis of CV risk associated with celecoxib (not funded by the manufacturer) was less comprehensive because it did not have access to all of the trial data.¹³⁶ It limited its analysis to trials that were at least 6 weeks duration and reported cardiovascular events in published articles or publically available material on the FDA or manufacturer website, and also differed from the Moore analysis by including trials of patients receiving celecoxib for colon polyp prevention and Alzheimer's disease. It found that the risk of myocardial infarction was increased in 3 trials (APC, ADAPT, PreSAP; none of arthritis patients) comparing celecoxib to placebo (OR 2.26, 95% CI 1.0 to 5.1) and in 5 trials (APC, CLASS, ADAPT, PreSAP, VACT; the latter 2 of arthritis patients) comparing celecoxib to placebo, diclofenac, ibuprofen, or paracetamol (OR 1.88, 95% CI 1.15 to 3.08) (Table 10). No heterogeneity was present. There was no association between celecoxib use and either cerebrovascular events, cardiovascular death, or composite cardiovascular events. Although this study was rated good quality, lack of comprehensiveness is a concern because it excluded 42 celecoxib trials either because they were shorter than 6 weeks or because publicly available information on cardiovascular events was not available. In addition, nearly two-thirds (18 of 29) of the myocardial infarctions in the placebo-controlled trials (the primary analysis) came from the APC (polyp prevention) trial. On the other hand, the meta-analysis also did not include the recently published, large (N=13,274), 12-week SUCCESS-I Study, which reported results consistent with its findings (10 myocardial infarctions or 0.55/100 patient-years in the combined celecoxib arms versus 1 myocardial infarction or 0.11/100 patient-years in the combined non-selective NSAID arms).⁶³

Table 10. MI's in trials of celecoxib: meta-analysis of trials of at least 6 weeks duration with published or publicly available data¹³⁶

Comparison	Relative risk for myocardial infarction
Celecoxib any dose versus placebo (3 trials)	2.3 (1.0 to 5.1)
Celecoxib any dose versus placebo, diclofenac, ibuprofen, or paracetamol	1.9 (1.2 to 3.1)

The fifth meta-analysis (also not funded by the manufacturer) analyzed data from 41 published and unpublished trials of celecoxib (8,976 patient-years of exposure).¹²⁹ Nine of the trials were longer than 12 weeks in duration. Characteristics of this study, which also evaluated cardiovascular risks associated with other selective and non-selective NSAIDs, are discussed in the rofecoxib section above. Data on celecoxib risk primarily came from patients with osteoarthritis or rheumatoid arthritis (33 trials), but studies of low back or temporomandibular joint pain, ankylosing spondylitis, Alzheimer's disease, and colon polyp prevention were also included. Myocardial infarction rates were higher with celecoxib relative to placebo (0.5% or 44/8976 person-years versus 0.2% or 9/4953, RR 2.13, 95% CI 1.20 to 3.80), and for combined vascular events (0.9% vs. 0.6%, RR 1.51, 95% CI 1.02 to 2.24), but there were no significant differences in risk of stroke alone or vascular death (Table 11). This is equivalent to approximately one additional myocardial infarction for every 325 patients treated with celecoxib instead of placebo for one year. The 99% confidence interval (reported in the article because of multiple subgroup analyses) remained significant for myocardial infarction, but not for combined vascular events. Two large polyp prevention trials accounted for about 60% (27 of 44) of the myocardial infarctions in patients randomized to celecoxib.¹⁰⁹ A trend towards increased risk of vascular events ($p=0.03$) with higher doses of celecoxib was present, but nearly all of the events at the highest (800 mg daily) dose occurred in the polyp prevention trials. Analyses on the effects of duration and independent event adjudication were not stratified by specific COX-2 inhibitor, nor were estimates of cardiovascular risk with specific COX-2 inhibitors relative to naproxen or non-naproxen NSAIDs (see section on CV risk of non-selective NSAIDs).

Table 11. CV events in trials of celecoxib: meta-analysis of 41 trials of at least 4 weeks duration¹²⁹

Comparison	Outcome	Relative risk (95% CI)
Celecoxib any dose versus placebo	Any vascular event	1.5 (1.0 to 2.2)
Celecoxib any dose versus placebo	Myocardial infarction	2.1 (1.2 to 3.8)
Celecoxib any dose versus placebo	Stroke	1.1 (0.6 to 2.2)
Celecoxib any dose versus placebo	Vascular death	1.3 (0.6 to 2.8)

The estimates of risk for myocardial infarction with celecoxib relative to placebo in the non-manufacturer-funded meta-analyses^{129, 136} are higher than in the manufacturer-funded meta-analyses.^{134, 135} The major reason for the difference in estimates appears to be the inclusion of two recent, long-term trials of colon polyp prevention (APC and PreSAP) in the former.^{108, 110} A large number of myocardial infarctions occurred in these trials (27, compared to a total of nine in the most comprehensive manufacturer-funded meta-analysis¹³⁵), and estimates of risk from both trials were higher than previous pooled estimates without these trials (RR 1.58, 95% CI 0.92 to 2.72).¹³⁵ In one meta-analysis,^{129, 136} the rate of nonfatal myocardial infarction was 1.3% (18/1356) with celecoxib (200 or 400 mg twice daily) versus 0.4% (3/679) with placebo (RR

2.67, 95% CI 0.5 to 8.41) in the APC trial¹⁰⁸ and 1.0% (9/933) versus 0.5% (3/628) for a relative risk of 1.84 (95% CI 0.54 to 6.28) in PreSAP (400 mg once daily).¹¹⁰ A subsequent analysis of the APC trial and PreSAP using slightly different data (due to the identification of additional events after study closure) reported a pooled relative risk of 1.9 (95% CI 1.1 to 3.1, no heterogeneity) for the composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure.¹⁰⁹ Rates of fatal or nonfatal myocardial infarction in were 1.6% (22/1356) versus 0.4% (3/679) in the APC trial and 9/933 (1.0%) vs. 4/628 (0.6%) in PreSAP.

In summary, celecoxib appears associated with an increased risk of myocardial infarctions or thromboembolic cardiovascular events relative to placebo. Much of the evidence for increased cardiovascular risk comes from two large, long-term polyp prevention studies comparing celecoxib 200 or 400 mg twice daily, or 400 mg once daily to placebo. Although trends toward increased myocardial infarction risk with celecoxib relative to placebo as well as relative to other NSAIDs are also present in meta-analyses of primarily short-term trials of arthritis patients, small numbers of events limit the precision of estimates from those trials.

Observational Studies of GI and CV Safety

Overview. Numerous long-term observational studies have evaluated the GI and CV risks associated with selective and non-selective NSAIDs. The studies primarily relied on claims data or other administrative databases or on electronic medical record data collected in practice networks to identify cases, and prescription claims to determine exposure. A strength of these studies is that they evaluated much larger populations than could be enrolled into clinical trials.¹³⁷ In addition, they reflect how coxibs and other NSAIDs are actually used in practice better than many clinical trials, which are usually short term, require rigid dosing regimens, limit the use of other drugs, and implement strategies to monitor and enhance compliance. Population- and practice-based studies may also better represent patients who would be excluded from randomized trials because of comorbidities, age, or other factors.

On the other hand, the most important weakness of observational studies is that patients are allocated treatment in a non-randomized manner. This can lead to biased estimates of effects even when appropriate statistical adjustment on a variety of confounding variables is performed.⁴⁰ In addition, data sources typically cannot reliably assess over-the-counter aspirin, NSAIDs, or acid-suppressing medication use,¹³⁷ and information on prescription fills may not always accurately correspond to the actual degree of exposure to the drugs.

Rofecoxib. Five observational studies reported rates of serious GI events for rofecoxib relative to celecoxib, NSAIDs, and non-use.¹³⁸⁻¹⁴² (Table 12). In direct comparisons, rofecoxib was associated with a similar risk of upper GI complications compared to meloxicam,¹⁴⁰ but a greater risk of upper GI hemorrhage than celecoxib, non-selective NSAIDs, and diclofenac plus misoprostol.^{139, 142} In a nested case-control study, the risk of upper GI bleeding was modestly higher for rofecoxib compared to celecoxib, NSAIDs, or non-use (RR in the range of 1 to 2.)¹³⁸ Another case-control study that reported higher relative risks of serious GI events with rofecoxib should be interpreted with caution because exposure information was ascertained using unblinded patient interviewing, which is more susceptible to recall bias than blinded coding of exposures status from prescription or general practice databases.¹⁴¹

Analyses of the effects of exposure duration, dosage, and study duration on risk of serious GI events were generally not reported. In fact, COX-2 dosages were only reported in one study

which reported that the proportion of patients on celecoxib receiving >200 mg/day was 19%, and the proportion of patients on rofecoxib on >25 mg/day was 8%.¹³⁹

Table 12. Serious GI events in observational studies

Author, Year Study design Sample size	Mean age (yrs)	Duration (days)	Outcome	Main findings
Hippisley-Cox 2005 ¹³⁸ Case-control Cases: 9407	NR; ≥ 25	Unclear	Complicated GI event	↑ <i>risk relative to non-use</i> : No for celecoxib (RR 1.25; 95% CI 0.91, 1.72) Yes for rofecoxib (RR 1.79; 95% CI 1.42, 2.26); overall selective (RR 1.72; 95% CI 1.29, 2.29) and non-selective NSAIDs (1.67; 95% CI 1.43, 1.94); ibuprofen (RR 1.58; 95% CI 1.37, 1.83); diclofenac (RR 2.07; 95% CI 1.82, 2.35); naproxen (RR 1.97; 95% CI 1.48, 2.61)
Mamdani 2002 ¹³⁹ Cohort n=143,969	75.7	141	Upper GI hemorrhage	↑ <i>risk relative to celecoxib</i> : Yes for rofecoxib (RR 1.9; 95% CI 1.2, 2.8), non-selective NSAIDs (RR 1.9; 95% CI 1.0, 3.5) and diclofenac+ misoprostol (RR 3.2; 95% CI 1.6, 6.5)
Layton 2003 ¹⁴⁰ Cohort n=34,355	60.4-62.5	270	Upper GI complications (perforations/bleeding)	Similar risk for rofecoxib and meloxicam (RR 0.91; 95% CI 0.59, 1.42)
Laporte 2004 ¹⁴¹ Case-control Cases=2,813	NR; ≥ 18	NR	Upper GI bleeding	↑ <i>risk vs. non-use</i> for rofecoxib (RR 7.2; 95% CI 2.3, 23.0), diclofenac (RR 3.7; 95% CI 2.6, 5.4), ibuprofen (RR 3.1; 95% CI 2.0, 4.9), indomethacin (RR 10.0; 95% CI 4.4, 22.6), ketoprofen (RR 10.0; 95% CI 3.9, 25.8), ketorolac (RR 24.7; 95% CI 8.0, 77.0), meloxicam (RR 5.7; 95% CI 2.2, 15.0), naproxen (RR 10.0; 95% CI 5.7, 17.6), nimesulide (RR 3.2; 95% CI 1.9, 5.6), piroxicam (RR 15.5; 95% CI 10.0, 24.2)
Kasliwal 2006 ¹⁴² Cohort n=32,726	62.5	Median Rofecoxib=111 Celecoxib=90 p<0.0001	Upper GI complications (perforations/bleeding)	Rofecoxib versus celecoxib aRR (95% CI): 1.60 (0.95, 2.70)

Fourteen observational studies evaluated the risk of cardiovascular events associated with rofecoxib (Table 13).¹⁴²⁻¹⁵⁵ Interpretation of the studies is complicated by the use of different study designs, adjustment for different confounders, and evaluation of different populations and outcomes. Six of these studies appeared to rely exclusively on administrative and pharmaceutical databases to determine outcomes, exposures, and comorbidities.^{143, 147, 149-152} The other studies supplemented administrative or claims data with chart review;^{145, 153} clinical or practice-based databases,^{146, 148, 155} or telephone interviews.¹⁴⁴ An interim analysis of one study relied on a combination of a medication surveillance database, physician questionnaires, hospital admission data, spontaneous reports, and national morbidity and mortality databases.¹⁵⁴

Several studies indicate that using claims data is quite accurate (positive predictive value >90%) for identifying myocardial infarction.^{156, 157} A weakness of relying exclusively on administrative databases, however, is that they frequently have incomplete information about potentially important confounders such as income level, obesity, smoking status, and level of

education.¹⁵⁷ All three of the observational studies that collected information about body mass index, for example, supplemented administrative databases with other sources.¹⁴⁴⁻¹⁴⁶ Unmeasured confounders could result in less accurate estimates of cardiovascular risk, though one analysis suggests that the effects would be only modest.¹⁵⁸ On the other hand, studies can also ‘overcontrol’ if they attempt to adjust for cardiovascular risk factors identified after the initiation of treatment, when the risk factors are actually intermediate effects of the drugs themselves that predispose to subsequent cardiovascular events.¹⁵⁹

Rofecoxib was associated with an increased risk of CV events relative to non-selective NSAIDs in three of five studies^{40, 144, 152, 153} and an increased risk relative to celecoxib in three of five studies.^{142, 144, 145, 154, 160} In studies that compared rofecoxib, celecoxib, or NSAID use to non-use, none of the drugs were consistently associated with increased risk of CV events.^{143, 146, 147, 149, 151, 155} CV event risk estimates from two observational studies of rofecoxib relative to naproxen (Solomon 2004¹⁴⁵: OR 1.17, 95% CI 0.90, 1.52; Kimmel 2005¹⁴⁴: OR 3.30, 95% CI 1.37, 8.40) were lower than the estimated relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen in VIGOR.¹⁰³ It is likely that the inconsistencies in effect magnitudes were due in large part to population differences and study methodology. For example, risk estimates from the Solomon 2004 study¹⁴⁵ may only be generalizable to a population that is of a more advanced age than that of VIGOR (81.6 vs. 58 years) and of a possibly lower income level, as it focused on low-income Medicare beneficiaries. Participants in the Kimmel 2005 study,¹⁴⁴ on the other hand, were similar in mean age to those in VIGOR (53.1 vs. 58 years), but different methods of data ascertainment may have affected risk estimates. This study, which found the highest risk of MI associated with rofecoxib compared with celecoxib (OR 2.72), differed from the others in that it collected information about exposures and covariates using structured telephone interviews rather than by using administrative or large practice databases.¹⁴⁴ The use of structured telephone interviews could have enhanced the ability of the investigators to measure relevant confounders and drug exposures. On the other hand, participation bias (only 50% of those approached participated) and recall bias could have skewed the results, though it is not clear that such biases should favor either rofecoxib or celecoxib.

Results of studies that found similar risk of CV events with rofecoxib and meloxicam¹⁵² or celecoxib^{142, 154} may also be less reliable. These studies adjusted for far fewer demographic and prognostic factors than other studies that adjusted for multiple demographic factors and comorbidities.

Another factor that varied between studies was how exposure status was defined. In one of the studies that reported no association between rofecoxib use and cardiovascular thrombotic events, use of selective COX-2 inhibitors was defined as prescriptions within 6 months of the index date.¹⁵⁰ By contrast, other studies defined current use as occurring on or near the index date, which strengthens confidence in inferences about the link between rofecoxib and the observed MIs.

Table 13. Cardiovascular events in observational studies

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Levesque 2005 ¹⁴³ Cohort n=59724	NR; ≥ 66	22.50%	844.8	Acute MI, fatal or nonfatal ↑ risk relative to NSAID non-use: Yes for rofecoxib, regardless of dose (Overall RR 1.24; 95% CI 1.05, 1.46) No for celecoxib (Overall RR 0.99; 95% CI 0.85, 1.16), naproxen (RR 1.17; 95% CI 0.75, 1.84) or meloxicam (95% CI 1.06; 95% CI 0.49, 2.30)
Kimmel 2005 ¹⁴⁴ Case-control Cases: 1718	NR; aged 40 to 75	33.60%	NR	Nonfatal MI ↑ risk for rofecoxib when directly compared with celecoxib (OR 2.72; 95% CI 1.24 to 5.95) or naproxen (OR 3.39; 95% CI 1.37, 8.40) ↑ risk for rofecoxib* relative to ibuprofen or diclofenac (OR 2.04; 95% CI 1.16, 3.60) or naproxen (OR 3.30; 95% CI 1.37, 8.40) Risk for celecoxib* similar to ibuprofen or diclofenac (OR 0.77; 95% CI 0.4, 1.48) or naproxen (OR 0.81; 95% CI 0.37, 1.77) *Regardless of aspirin use
Solomon 2004 ¹⁴⁵ Case-control Cases=10,895	NR; > 80	NR	1-30 days 31-90 days > 90 days	Acute MI ↑ risk for rofecoxib relative to celecoxib (OR 1.24; 95% CI 1.05, 1.46) Risk for rofecoxib similar to naproxen (aOR 1.17; 95% CI 0.9, 1.52) or ibuprofen (aOR 1.21; 95% CI 0.92, 1.58) or other NSAIDs (aOR 1.17; 95% CI 0.99, 1.38) Risk for celecoxib similar to naproxen (aOR 0.95; 95% CI 0.74, 1.21) or ibuprofen (aOR 0.98; 95% CI 0.76, 1.26) or other NSAIDs (aOR 0.95, 95% CI 0.82, 1.10)
Hippisley-Cox 2005 ¹⁴⁶ Case-control Cases: 9218	NR; aged 25-100	NR	NR	First ever MI ↑ risk relative to nonuse: Yes for rofecoxib (aOR 1.32; 95% CI 1.09, 1.61), other selective NSAIDs (aOR 1.27; 95% CI 1.00, 1.61), ibuprofen (aOR 1.24; 95% CI 1.11, 1.39), diclofenac (aOR 1.55; 95% CI 1.39, 1.72), naproxen (aOR 1.27; 95% CI 1.01, 1.60) and other non-selective NSAIDs (aOR 1.21; 95% CI 1.02, 1.44) No for celecoxib (aOR 1.21; 95% CI 0.96, 1.54)
Mamdani 2003 ¹⁴⁷ Cohort n=166,964	NR; ≥ 66	14.70%	165.6	Incidence of hospitalization for acute MI: risk relative to non-use Similar risk for rofecoxib (aRR 1.0; 95% CI 0.8, 1.4), celecoxib (aRR 0.9; 95% CI 0.7, 1.4), naproxen (aRR 1.0; 95% CI 0.6, 1.7), or non-naproxen non-selective NSAIDs (aRR 1.2; 95% CI 0.9, 1.4)
Graham 2005 ¹⁶⁰ Case-control Cases=8,143	NR: 18-84	Telephone interview subgroup (n=817): 23%	Mean=113 days before event	Acute MI requiring admission or sudden cardiac death: risk relative to celecoxib ↑ risk for rofecoxib for all dosages (aOR 1.59; 95% CI 1.10, 2.32) or for dosages > 25 mg (aOR 3.58; 95% CI 1.27, 10.11), but dosages ≤ 25 mg had risk similar to celecoxib (aOR 1.47; 95% CI 0.99, 2.17) ↑ risk for ibuprofen (aOR 1.26; 95% CI 1.00, 1.60), naproxen (aOR 1.36; 95% CI 1.06, 1.75), or other NSAIDs (aOR 1.35; 95% CI 1.06, 1.72)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Johnsen 2005 ¹⁴⁹ Case-control Cases=10,280	69.6	6.9% high dose	NR	Acute MI: risk relative to nonusers ↑ risk current (aRR 1.80; 95% CI 1.47, 2.21) and new users (aRR 2.52; 95% CI 1.45, 3.13) of rofecoxib ↑ risk for new users of celecoxib (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62) Similar risk for new (aRR 1.65; 95% CI 0.57, 4.83) or current users of naproxen (aRR 1.50; 95% CI 0.99, 2.29) relative to nonuse ↑ risk for new (aRR 2.65; 95% CI 2.00, 3.50) or current users of other nonaspirin NSAIDs (aRR 1.68; 95% CI 1.52, 1.85) naproxen (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62)
Shaya 2005 ¹⁵⁰ Cohort n=6,250 50% black	NR; 70% were aged 50 years or younger	NR	≥ 60 prior to event	Cardiovascular thrombotic events: relative to non-naproxen NSAIDs Similar for rofecoxib (aOR 0.99; 95% CI 0.76, 1.30) or celecoxib (aOR 1.19; 95% CI 0.93, 1.51)
Ray 2002 ¹⁵¹ Cohort n=378,776	61.5	NR	NR	Serious CHD (hospital admission for AMI or death from CHD): relative to non-use Similar risks for rofecoxib at dosages ≤ 25 mg (aIRR 1.03; 95% CI 0.78, 1.35) or > 25 mg (aIRR 1.70; 95% CI 0.98, 2.95), celecoxib (aIRR 0.96; 95% CI 0.76, 1.21), ibuprofen (aIRR 0.91; 95% CI 0.78, 1.06), or naproxen (aIRR 0.93; 95% CI 0.82, 1.06) relative to nonuse
Layton 2003 ¹⁵² Cohort n=34,355	NR	NR	270	Thromboembolic events: Rofecoxib vs meloxicam (A) cardiovascular: similar risk (RR 1.38; 95% CI 0.71, 2.67) (B) cerebrovascular: increased risk with rofecoxib (RR 1.68; 95% CI 1.15, 2.46) (C) peripheral venous thrombotic: lower risk for rofecoxib (RR 0.29; 95% CI 0.11, 0.78)
Velentgas 2005 ¹⁵³ Cohort n=424,584	NR (40-64 years)	NR	5.1 months	Combined endpoint of acute coronary syndrome and myocardial infarction: risk relative to ibuprofen or diclofenac (adjusted rate ratios) Increased risk for current use of rofecoxib (1.35; 95% CI 1.09, 1.68) and but not for recent use (1.15; 95% CI 0.88, 1.50) No increased risk for current (1.03; 95% CI 0.83, 1.27) or recent use of celecoxib (0.91; 95% CI 0.70, 1.17) No increased risk for current (1.14 95% CI 0.93, 1.39) or recent use of naproxen (0.86; 95% CI 0.70, 1.04)
Harrison-Woolrych 2005 ¹⁵⁴ Cohort Interim analysis of 11,149 of 58,849 who completed follow-up by 11/30/04	NR	NR	NR	Thrombotic cardiovascular events Celecoxib and rofecoxib were associated with similar risks (aHR 0.94; 95% CI 0.51, 1.70)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Andersohn 2006 ¹⁵⁵ Case-control Cases=3,643	68.7	NR	Mean=542 days	aRR (95% CI) for diagnosis of AMI, death from AMI, or sudden death from coronary heart disease (CHD) relative to nonuse: Increased risk for celecoxib 1.56 (1.23, 1.98), rofecoxib 1.33 (1.06, 1.67), etoricoxib 2.02 (1.08, 3.80) and diclofenac 1.36 (1.17, 1.58) No increased risk for valdecoxib 4.26 (0.60, 30.27), ibuprofen 1.00 (0.83, 1.21) or naproxen 1.16 (0.86, 1.58)
Kasliwal 2006 ¹⁴² Cohort n=32,726	62.5	Rofecoxib=35.3% Celecoxib=21.9% P<0.0001	Median Rofecoxib=111 Celecoxib=90 p<0.0001	aRR (95% CI) for rofecoxib versus celecoxib (adjusted for age, sex, and concomitant use of the combination of aspirin and/or antiplatelet/anticoagulant agents (a) Cardiovascular TE: 1.04 (0.50, 2.17) (b) Cerebrovascular TE: 1.43 (0.86, 2.38) (c) Peripheral venous (DVT/PE): 0.36 (0.01, 1.34)

aOR=adjusted odds ratio; aRR=adjusted relative risk; aIRR=adjusted incidence rate ratios; aHR=adjusted hazard ratio;
CI=confidence interval

Celecoxib. As summarized above, celecoxib was consistently associated with lower risks of serious GI¹³⁹ and CV events^{144, 145, 160} than rofecoxib in several observational studies. Observational studies also demonstrated that, compared with non-selective NSAIDs, celecoxib was consistently GI protective^{139, 162} or neutral¹³⁸ and was never associated with higher risks of CV events.^{144, 145, 150, 160}

Specifically, with regard to GI safety, celecoxib was associated with significantly lower risks of GI hemorrhage when directly compared to non-selective NSAIDs (relative risk 0.23, 95% CI 0.12, 0.43)¹³⁹ and of perforation or bleeding compared to meloxicam (RR 0.56; 95% CI 0.32, 0.96).¹⁶² Risk of complicated GI events was significantly lower for NSAID nonuse relative to numerous NSAIDs (i.e., selective NSAIDs, ibuprofen, diclofenac, naproxen, non-selective) but was similar relative to celecoxib.¹³⁸

With regard to CV safety, celecoxib was associated with similar risks (estimate range 0.77 to 1.19) of serious CV events compared to ibuprofen, diclofenac, naproxen, and "other NSAIDs"^{144, 145, 150} and, in one study, was associated with significantly lower risks of acute MI requiring admission or sudden cardiac death than ibuprofen, naproxen, or other NSAIDs.¹⁶⁰

Relative to non-use, some observational studies have shown an increased risk of MI associated with celecoxib^{149, 155}, whereas others have not.^{143, 146, 147} In the two studies that found an association, the increased MI risk was either time-dependent¹⁴⁹ or dose-dependent.¹⁵⁵

Additional analysis of observational studies. An important limitation of the observational studies is that they did not simultaneously assess the risk for serious cardiac and GI events. We re-analyzed data from three studies that reported rates of acute myocardial infarction,¹⁴⁷ hospital admissions for congestive heart failure,¹⁶³ and upper gastrointestinal bleeding¹³⁹ in a large cohort of elderly patients in Ontario, Canada, to estimate the net effects of selective and non-selective NSAIDs on serious cardiovascular and GI events in this population. Although the three studies evaluated the cohort at slightly different points in time, study methods and populations characteristics appeared essentially identical.

We calculated the effects of selective and non-selective NSAIDs on numbers of acute myocardial infarction, upper GI bleed, and hospitalization for heart failure using baseline rates of events in patients not exposed to NSAIDs and estimates of risk as reported in the studies (Table 14). We then estimated the net effects on all three serious adverse events using Monte Carlo simulation (see Methods section for additional details).

Table 14. Baseline rates of MI, upper GI bleed, and congestive heart failure (CHF) and risk associated with selective and non-selective NSAIDs in an Ontario cohort of elderly persons

Adverse event	Study, year	Baseline rates (per 1000 person-years)	Risk with celecoxib	Risk with rofecoxib	Risk with non-selective NSAIDs	Risk with naproxen
Myocardial infarction	Mamdani, 2003 ¹⁴⁷	8.2	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.4)	1.5 (1.2 to 1.8)	1.0 (0.6 to 1.7)
Upper GI bleed	Mamdani, 2002 ¹³⁹	2.2	1.0 (0.7 to 1.6)	1.9 (1.3 to 2.8)	4.0 (2.3 to 6.9)	4.0 (2.3 to 6.9)
Heart failure admission	Mamdani, 2004 ¹⁶³	9.1	1.0 (0.8 to 1.3)	1.8 (1.5 to 2.2)	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.9)

Our results (see Table 15) suggest that in this population, under real-world conditions, use of celecoxib was neutral with regard to these adverse events when compared with non-use. On the other hand, use of rofecoxib, non-selective NSAIDs, and naproxen were all associated with more serious adverse events than they prevented (Table 15). Rofecoxib and naproxen essentially appeared equivalent when considering all three adverse events together, though rofecoxib was associated with more heart failure admissions and fewer GI bleeds. Our estimates are consistent with analyses of serious adverse events in VIGOR (discussed earlier), which found that rates were essentially equivalent for rofecoxib and non-selective NSAIDs.^{113, 114} However, the result are discordant from analyses of serious adverse events in CLASS, which found that celecoxib offered no advantage over non-selective NSAIDs.^{94, 113} Differences in populations (the Ontario cohort only enrolled patients over 65 years old who filled multiple prescriptions), indications for starting celecoxib, dosing of celecoxib, or co-medication use might account for this discrepancy. In addition, because these studies only included patients who filled multiple prescriptions for NSAIDs, the analyses could underestimate early adverse events.

Table 15. Effects of selective or non-selective NSAIDs on number of serious adverse events

	Estimated effect on MI's (number per 1000 person-years)	Estimated effect on GI bleed (number per 1000 person-years)	Estimated effect on heart failure admissions (number per 1000 person-years)	Net effect on number of MI's, GI bleeds, and heart failure admissions (number per 1000 person-years)
Celecoxib	-0.82 (-2.46 to 1.64)	0 (-0.66 to 1.32)	0 (-1.82 to 2.73)	-0.70 (-3.58 to 2.71)
Rofecoxib	0 (-1.64 to 3.28)	+1.98 (0.66 to 3.96)	+7.28 (4.55 to 10.92)	+9.42 (5.47 to 13.99)
Non-selective NSAIDs	+4.1 (1.64 to 6.56)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+14.68 (8.59 to 22.72)
Naproxen	0 (-3.28 to 5.74)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+10.77 (3.92 to 19.89)

GI and CV Safety of Valdecoxib

The risk of clinically significant upper GI events (bleeding, perforation, and gastric outlet obstruction) with valdecoxib was evaluated in a fair-quality, manufacturer-funded meta-analysis of eight randomized controlled trials of 12 to 26 weeks duration.¹¹⁷ This study prospectively defined ulcer complications and used independent adjudication to determine adverse events. However, it is not described how assiduously the trials adhered to the adjudication process. Four of the trials were not published, and there was insufficient information about study design to determine the quality of the trials. The meta-analysis found valdecoxib associated with a significantly lower rate of significant upper GI events compared with non-selective NSAIDs (0.68% vs. 1.96%, all patients; 0.29% vs. 2.08%, non-aspirin users; $p < 0.05$). Another meta-analysis of five trials by the same authors found valdecoxib associated with a lower risk of 'moderate-to-severe' upper GI symptoms compared with non-specific NSAIDs (HR 0.59, 95% CI 0.47 to 0.74) and similar risk relative to placebo.¹⁶⁴ Adverse events were self-reported by patients in these trials, and the quality of the trials was not assessed by the meta-analysts. Two of the included trials were published only in abstract form.

We found no published trials evaluating the risk of cardiovascular events associated with valdecoxib in patients with arthritis. Valdecoxib was not associated with an increased risk of cardiovascular events relative to placebo or other NSAIDs in any of three fair-quality meta-analyses of primarily unpublished data. The ability to detect increased cardiovascular risk in all of these meta-analyses is limited by small numbers of events. A meta-analysis funded by Pfizer and presented to the FDA in February 2005 analyzed primarily unpublished data from 19 trials of patients with chronic pain (methods described above in the section on celecoxib).¹³⁵ Thirteen studies were of patients with osteoarthritis or rheumatoid arthritis. Three were longer than 12 weeks in duration. There was no association between valdecoxib use and either cardiovascular thromboembolic events or myocardial infarction (Table 16). However, only 5 of 4,438 patients (0.2%) randomized to valdecoxib in the placebo-controlled trials and 6 of 4,591 (0.1%) in the active-controlled trials had a cardiovascular event. An earlier meta-analysis of 10 trials (also funded by Pfizer, and using similar methods) also found no difference in risk for myocardial infarction between valdecoxib and either placebo or other NSAIDs.¹³⁴

Table 16. Myocardial infarction in trials of valdecoxib for chronic pain: meta-analysis of 19 trials¹³⁵

Comparison	Relative risk for myocardial infarction
Valdecoxib ≥ 10 mg/day versus placebo	1.80 (0.47-6.97)
Valdecoxib ≥ 10 mg/day versus non-selective NSAID	0.32 (0.12-0.87)

The most recent meta-analysis (not funded by the manufacturer) included 14 placebo-controlled trials (Table 17).¹²⁹ There were no significant differences between valdecoxib and placebo for the outcomes any vascular event (RR 1.47, 95% CI 0.44 to 4.95), myocardial infarction (RR 1.65, 95% CI 0.28 to 9.87), stroke (RR 0.85, 95% CI 0.07 to 10.6) or vascular death (RR 2.72, 95% CI 0.49 to 15.2). A total of 14 vascular events (1.9%) and 8 myocardial infarctions (1.1%) occurred among the 748 patients in the valdecoxib arms.

Table 17. Cardiovascular events in trials of valdecoxib versus placebo: meta-analysis of 14 trials¹²⁹

Comparison	Outcome	Relative risk
Valdecoxib versus placebo	Any vascular event	1.47 (0.44-4.95)
Valdecoxib versus placebo	Myocardial infarction	1.65 (0.28-9.87)
Valdecoxib versus placebo	Stroke	0.85 (0.07-10.6)
Valdecoxib versus placebo	Vascular death	2.72 (0.49-15.2)

None of the meta-analyses included two short-term (<2 month) trials in the high-risk setting of post-coronary artery bypass surgery.^{165,166} In these trials, parecoxib (an intravenous coxib rapidly converted to valdecoxib) followed by valdecoxib (40 mg bid¹⁶⁵ or 20 mg bid¹⁶⁶) was associated with a two- to three-fold higher short-term risk of cardiovascular events compared with placebo (pooled relative risk 3.08, 95% CI 1.20 to 7.87).¹⁶⁷

FDA information. A warning was added to the valdecoxib product label in November, 2002. It was prompted by reports of cases of serious anaphylactic reactions and serious dermatologic adverse events in postmarketing surveillance.¹⁶⁸ A study of two large European data sources and the US FDA spontaneous adverse events reporting system prior to the introduction of COX-2 inhibitors found other NSAIDs—in particular piroxicam and tenoxicam—also associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.¹⁶⁹ However, the rates of these events were extremely low, on the order of one per 100,000 or less during an initial 8-week course of therapy.

GI and CV Safety of Etoricoxib

A fair quality meta-analysis of ten RCTs, which included long-term (>1 year) data from 7 trials of OA, RA, or ankylosing spondylitis patients, found etoricoxib at doses ranging from 5 to 120 mg/day (mean dose 87 mg/day) associated with a lower risk of confirmed PUBs (upper GI perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding) compared to diclofenac 150 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day (1.24% vs. 2.48%, RR 0.48, 95% CI 0.32, 0.73).¹⁷⁰ This meta-analysis was rated fair quality because it did not provide adequate detail of the included trials and did not evaluate the effects of dose, duration, or other potential sources of heterogeneity. In addition, it included results of noncomparative extension phases in its analyses, resulting in unequal durations of follow-up for the etoricoxib group (median 12.4 months) compared to the non-selective NSAID groups (median 6.3 months). There were too few events in patients on concomitant aspirin (8 overall) to evaluate its effects on GI safety. An earlier meta-analysis that used similar methods to analyze rates of perforations, symptomatic ulcers, and bleeds reported similar results.¹⁷¹

There is only limited evidence regarding the CV risk associated with long-term use of etoricoxib. One 52-week trial reported that no patients randomized to naproxen and five (2%) randomized to etoricoxib (four receiving 90 mg/day; one 120 mg/day) experienced a serious cardiovascular adverse event.¹⁷²

Three meta-analyses have evaluated cardiovascular risks associated with etoricoxib. The largest and most recent meta-analysis (by Kearney and colleagues) included 17 placebo-controlled trials of patients (1,167 person-years of exposure) mainly with osteoarthritis or rheumatoid arthritis.¹²⁹ Most of the trials had short (less than 12 weeks) placebo-controlled periods. There was no difference between etoricoxib and placebo for risk of any vascular event (RR 1.78, 95% CI 0.43 to 7.40), myocardial infarction (RR 4.48, 95% CI 0.20 to 99.4), stroke

(RR 1.17, 95% CI 0.21 to 6.51), or vascular death (RR 4.48, 95% CI 0.36 to 56.3). The number of cardiovascular events was very low, with only two myocardial infarctions over 753 person-years of exposure to etoricoxib (0.3%). A less-comprehensive systematic review of five short-term trials (all included in the Kearney meta-analysis) also found no significant increased risk of thromboembolic event (pulmonary embolism, deep vein thrombosis, myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack) with etoricoxib (dose range 30 to 90 mg) versus placebo (OR 1.49, 95% CI 0.42-5.31).¹⁷³ A third meta-analysis (available only as an abstract) of 12 trials of unspecified durations found that the cardiovascular safety of etoricoxib compared favorably to placebo and non-selective NSAIDs (RR 1.11, 95% CI 0.32, 3.81 and RR 0.83, 95% CI 0.26, 2.64, respectively) though there was a trend towards increased risk compared to naproxen (RR 1.70, 95% CI 0.91,3.18).¹⁷⁴

GI and CV Safety of Lumiracoxib

One large (N=18,325), long-term (52 weeks) study of osteoarthritis patients (The Therapeutic Arthritis Research and Gastrointestinal Event Trial, or TARGET) compared the safety of a supratherapeutic dose of lumiracoxib (400 mg/day) to naproxen (1000 mg/day) or ibuprofen (2400 mg/day) over 52 weeks.¹⁷⁵⁻¹⁷⁷ In patients not taking aspirin, lumiracoxib was associated with a lower risk of bleeding, perforation, or obstruction compared to naproxen or ibuprofen (HR 0.21, 95% CI 0.12, 0.37, 1-year incidence of ulcer complications 0.25% vs. 1.09%).¹⁷⁵ There was no difference in ulcer complication risk among aspirin users (HR 0.79, 95% CI 0.40, 1.55). The rate of myocardial infarction was low, ranging from 0.16% to 0.38%, and there were no statistically significant differences between interventions (HR 1.77 for lumiracoxib versus naproxen, 95% CI 0.82, 3.84 and HR 0.66 for lumiracoxib versus ibuprofen, 95% CI 0.21, 2.09).¹⁷⁷

A recent fair-quality meta-analysis of 12 primarily short-term trials found no significant increase in risk of vascular events (RR 1.13, 95% CI 0.43 to 2.93), myocardial infarction (RR 1.07, 95% CI 0.20 to 5.63), stroke (RR 0.63, 95% CI 0.13 to 3.11), or vascular death (RR 2.55, 95% CI 0.54 to 12.0) with lumiracoxib relative to placebo.¹²⁹ The number of events, however, was low, with only five myocardial infarctions among 1375 patients in the lumiracoxib arms (0.4%).

GI and CV Safety: Comparison of NSAIDs

Partially selective NSAIDs. Evidence that meloxicam, nabumetone, and etodolac prevent ulcer complications is weaker than that for coxibs. Meloxicam is the most widely studied of the three drugs and was generally associated with no advantage in GI protection relative to other partially-selective and non-selective NSAIDs or non-use.^{143, 178-185} Evidence for nabumetone and etodolac is sparse and insufficient to make reliable judgments about comparative GI and CV safety.

Meloxicam. Risks of serious ulcer complications (perforation, bleeding, or obstruction) and/or MI were reported in one clinical trial of meloxicam¹⁷⁹ and three observational studies.^{143, 180, 182} In the single, poor-quality (non-randomized and non-blinded) trial, meloxicam was not associated with significant differences in rates of GI hemorrhage at 6 months relative to other NSAIDs (RR 0.32; 95% CI 0.06, 1.63) in 4,526 rheumatoid arthritis patients seen by family or internal medicine physicians in Germany between August 1996 and July 1997.¹⁷⁹ However,

differences in baseline disease severity could have favored the control group, and it is unclear whether the analyses adjusted for such baseline differences. Estimates of GI and CV risk have also been reported in two recent (2004) cohort studies that followed participants for 14 months¹⁸⁰ and 2.4 years.¹⁴³ GI complication-related hospitalizations were similar for meloxicam (0), nabumetone (1, 4.5%), salsalate (1, 5.9%), naproxen (5, 7.9%), and ibuprofen (0) among a cohort of long-term care residents in Indiana (mean age=81.2 years).¹⁸⁰ In a cohort of 59,724 elderly individuals in Quebec, meloxicam (adjusted rate ratio 1.06; 95% CI 0.49, 2.30) and naproxen (1.17; 95% CI 0.75, 1.84) were associated with similar increases in risk of MI relative to non-use.¹⁴³ Meloxicam (RR 1.5; 95% CI 0.1, 17.1), naproxen (RR 1.0; 95% CI 0.3, 3.3), and piroxicam (RR 0.7; 95% CI 0.2, 2.3) were also associated with similar nonsignificant risks of MI relative to diclofenac in a nested case-control study using data from the UK GPRD.¹⁸²

Estimates of GI risk as measured by a composite score that included GI tolerability, PUBs, hospitalization or GI-related death outcomes were reported in a good-quality meta-analysis.¹⁸³ Compared to non-use, the composite GI risk for meloxicam (RR 1.24; 95% CI 0.98, 1.56) was comparable with that of non-selective NSAIDs. Relative risks of GI hospitalizations or GI-related deaths alone were not reported. Composite GI outcome data from cohort studies were also analyzed in this study and suggested higher risk estimates (combined NSAID RR 2.2, 95% CI 1.7, 2.9) than the trials, but the results were not stratified by individual NSAIDs.

Three meta-analyses focussing only on short-term trials reported PUBs (perforation, symptomatic ulcer, or bleeding) associated with meloxicam. The first meta-analysis included 10 trials (seven double-blinded).¹⁸¹ Most of the patients were followed for only 4 weeks, and the dose of meloxicam was 7.5 mg in 4 trials and 15 mg in 6 trials. The meta-analysis did not report absolute event rates, but found that the risk of PUBs was reduced in the meloxicam patients (OR 0.52, 95% CI 0.28-0.96) relative to non-selective NSAIDs. A twelve-week double-blind trial of meloxicam 7.5, 15 or 22.5 mg and diclofenac 75 mg bid in RA patients (n=894) published after this meta-analysis found similar PUB rates (1.1%, 0.5%, 0.6%, and 0%, respectively) in all arms.¹⁷⁸ In a more recent meta-analysis funded by the manufacturer of meloxicam and using manufacturer-held documents from 28 trials, there was a dose-response relationship between meloxicam and PUBs as ascertained by a blinded, external adjudication committee.¹⁸⁶ Meloxicam at 7.5 mg was associated with lower PUB rates during the first 60 days compared to diclofenac, piroxicam, or naproxen, but the 15 mg dose was only associated with lower PUB rates than piroxicam. In a third meta-analysis (not yet published) of three short-term (4- to 6-week) trials, there was no difference in the risk of complicated ulcers (perforations, obstructions and bleeds) associated with meloxicam relative to the non-selective NSAIDs piroxicam (two trials^{47, 52}) and diclofenac (one trial⁴⁹), with a relative risk of 0.50 (95% CI 0.23, 1.12).¹¹⁵

Nabumetone. For nabumetone, a fair-quality meta-analysis of six short-term (3 to 6 months) studies (five published and one abstract) found one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 non-selective NSAID patients; this result was highly statistically significant.¹⁸⁷ The absolute PUB rates were about 2 versus 6 per 1,000 patient-years. For comparison, in a similar meta-analysis of rofecoxib studies, the PUB rates per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs;¹¹⁸ it is not clear why the rates of PUBs were so much lower in the nabumetone trials. There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patients per year vs. 20.3 per 1,000 patients per year). The results of this meta-analysis are not directly comparable to other trials and meta-analyses that reported complicated ulcers as a separate outcome because

symptomatic ulcers were also included. In addition, the methods used to ascertain the endpoints in the trials were not described in enough detail to determine whether they were accurate and applied consistently. Finally, the similarity of the subjects in the efficacy trials to a broader group of NSAID users could not be determined.

Etodolac. We found no trials reporting rates of serious GI complications in patients taking etodolac. In two observational studies, etodolac was not associated with a lower rate of PUBs compared to non-use¹⁸⁴ or naproxen.¹⁸⁸ In another observational study using data from the UK General Practice Database, the adjusted relative risks of PUB compared with non-use ranged from 2.2 (95% CI 0.4, 11.3) for etodolac to 6.2 (95% CI 3.7, 10.1) for piroxicam and overlapped across all NSAIDs studied.¹⁸⁹ When compared to naproxen using historical data from Dallas Veterans Affairs Medical Center records, etodolac had a GI protective effect for all users (RR 0.24, 95% CI 0.09, 0.63) and for NSAID-naïve users (RR 0.18, 95% CI 0.05, 0.61) only when low-dose aspirin was not taken concomitantly.¹⁸⁸

Non-selective NSAIDs - GI safety. Randomized controlled trials¹¹⁵ and observational studies^{11, 190, 191} consistently report that non-selective, non-aspirin NSAIDs are associated with increased risks of serious GI events relative to non-use. There is no clear, consistent evidence that any one non-selective, non-aspirin NSAID is any less risky than another.

Preliminary results (not yet published) from a meta-analysis of randomized controlled trials found that selective COX-2 inhibitors as a class (defined by the investigators as celecoxib, rofecoxib, valdecoxib, lumiracoxib, and meloxicam) were associated with lower risks of complicated ulcers (perforation, obstruction, or bleed) when compared with naproxen (0.34; 95% CI 0.24, 0.48), ibuprofen (0.46; 95% CI 0.30, 0.70), and diclofenac (0.31; 95% CI 0.06, 1.61).¹¹⁵ There were no clear differences among the three non-selective NSAIDs. The validity of these findings, however, cannot be assessed until the full report is published. However, they are consistent with results from a previous meta-analysis in which increased risks of GI complications (major plus minor) were similar for different NSAIDs relative to non-use: indomethacin (RR 2.25; 95% CI 1.01, 5.07), naproxen (RR 1.83; 95% CI 1.25, 2.68), diclofenac (RR 1.73; 95% CI 1.21, 2.46), piroxicam (RR 1.66; 95% CI 1.14, 2.44), tenoxicam (RR 1.43; 95% CI 0.40, 5.14), meloxicam (RR 1.24; 95% CI 0.98, 1.56) and ibuprofen (RR 1.19; 95% CI 0.93, 1.54).¹⁸³

In an earlier, collaborative meta-analysis of cohort and case-control studies published between 1985 and 1994, use of all non-selective NSAIDs were associated with significantly increased risks of peptic ulcer complication hospitalizations relative to non-use.¹⁹⁰ Ibuprofen, at doses used in general practice, was associated with the lowest risk of peptic ulcer complication-related hospitalizations.¹⁹⁰ In a subsequent meta-analysis of cohort and case-control studies published between 1990 and 1999, however, risk of serious GI event-related hospitalizations and specialist visits was dose-dependent, and was no lower for ibuprofen compared to any other non-aspirin, non-selective NSAID when results were stratified by low to medium (RR 2.1, 95% CI 1.6, 2.7) or high dose (RR 5.5, 95% CI 3.0, 10.0) (Table 18).^{184, 191} A more recent review of observational studies published through 2002 also found GI bleeding risk increased for all non-selective NSAIDs, and risk appeared related more to dose than to the specific drug evaluated.¹¹

Table 18. Relative Risk (95% CI) of UGIB* for NSAIDs vs. non-use

	Hernandez-Díaz 2000 ¹⁹¹			Garcia-Rodriguez 2001 ¹⁸⁴
	Dose			Overall
NSAID	Overall	Low-Medium	High	
Diclofenac	3.3 (2.8, 3.9)	3.1 (2.0, 4.7)	3.6 (2.3, 5.6)	4.6 (3.6, 5.8)
Ibuprofen	1.9 (1.6, 2.2)	2.1 (1.6, 2.7)	5.5 (3.0, 10.0)	2.5 (1.9, 3.4)
Indomethacin	4.6 (3.8, 5.5)	3.0 (2.2, 4.2)	6.5 (4.8, 8.6)	5.2 (3.2, 8.3)
Ketoprofen	4.6 (3.3, 6.4)	NR	NR	3.3 (1.9, 5.9)
Naproxen	4.0 (3.5, 4.6)	3.5 (2.8, 4.3)	5.1 (3.8, 6.9)	4.0 (2.8, 5.8)
Piroxicam	6.3 (5.5, 7.2)	5.6 (4.7, 6.7)	6.2 (4.4, 8.7)	6.2 (3.7, 10.1)
Sulindac	3.6 (2.8, 4.7)	NR	NR	NR

*Upper GI tract bleeding/perforation

Non-selective NSAIDs were also associated with an increased risk of serious GI events in more recent observational studies. Ibuprofen (Odds Ratio 1.42, 95% CI 1.27, 1.59), diclofenac (OR 1.96; 95% CI 1.78, 2.15) and naproxen (OR 2.12, 95% CI 1.73, 2.15) were all associated with increased risks of GI hemorrhage, perforation, surgery or undefined uncomplicated events relative to non-use in a case-control study of the UK General Practice Research Database.¹³⁸ Odds ratios for upper GI events resulting in hospitalization associated with NSAIDs relative to non-use ranged from 3.1 (95% CI 2.0, 4.9) for ibuprofen to 24.7 (95% CI 8.0, 77.0) for ketorolac based on data from 10 hospitals in Spain using a case-control design.¹⁴¹

Non-selective NSAIDs – CV Safety

Randomized controlled trials. Evidence regarding the comparative risk of serious CV events for non-selective NSAIDs is more limited than the evidence for selective COX-2 inhibitors. In particular, long-term clinical trials are lacking. A recent, fair-quality meta-analysis by Kearney and colleagues of 91 trials (mostly ranging from 4 to 13 weeks in duration) evaluated risks with any non-selective NSAID (33,260 person-years of exposure) compared to any COX-2 inhibitor (23,325 person-years of exposure).¹²⁹ Most of the trials evaluated naproxen (42 trials), ibuprofen (24 trials), and diclofenac (26 trials); only 7 evaluated other non-selective NSAIDs. Generalizability to usual practice could be limited because the majority of the trials evaluated higher than standard doses of NSAIDs. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. Other characteristics of this meta-analysis are discussed in more detail in the section on cardiovascular risks associated with rofecoxib.

Table 19 shows estimates of risk for different cardiovascular outcomes with COX-2 inhibitors relative to non-selective NSAIDs. Risk of myocardial infarction was similar with COX-2 inhibitors and non-naproxen NSAIDs, but about two-fold greater for COX-2 inhibitors compared to naproxen (0.6% or 99/16360 vs. 0.3% or 30/10,978, RR 2.04, 95% CI 1.41 to 2.96). This is equivalent to about one additional myocardial infarction for every 301 patients treated for one year with a COX-2 inhibitor instead of naproxen. COX-2 inhibitor use was also associated with a lower risk of stroke relative to non-naproxen NSAIDs (RR 0.62, 95% CI 0.41 to 0.95). In subgroup analyses of specific non-selective NSAIDs (ibuprofen, diclofenac, other non-selective NSAIDs), the difference in stroke risk was only observed with diclofenac, which was usually evaluated at high doses (RR 0.48, 95% CI 0.27 to 0.83). There was insufficient data to analyze the effects of lower doses on estimates of risk.

Table 19. Rate Ratios (95% CI)*: COX 2 inhibitor relative to non-selective NSAID¹²⁹

NSAID group	Vascular events	Myocardial Infarction	Stroke	Vascular Death
Any non-selective NSAID	1.16 (0.97 to 1.38)	1.53 (1.19 to 1.97), p=0.0009	0.83 (0.62 to 1.12)	0.97 (0.69 to 1.35)
Any non-naproxen, non-selective NSAID	0.88 (0.69 to 1.12)	1.20 (0.85 to 1.68)	0.62 (0.41 to 0.95), p=0.03	0.67 (0.43 to 1.06)
Naproxen	1.57 (1.21 to 2.03)	2.04 (1.41 to 2.96), p=0.0002	1.10 (0.73 to 1.65)	1.47 (0.90 to 2.40)

*Rate ratios below 1 favor COX 2 inhibitors and rate ratios above 1 favor NSAIDs

Kearney and colleagues found insufficient data to directly estimate risks of non-selective NSAIDs from placebo-controlled trials. Indirect analyses (based on trials of non-selective NSAIDs versus COX-2 inhibitors and trials of COX-2 inhibitors versus placebo) suggest an increased risk of vascular events with ibuprofen (RR 1.51, 95% CI 0.96 to 2.37) and diclofenac (RR 1.63, 95% CI 1.12 to 2.37) relative to placebo, but not with naproxen (RR 0.92, 95% CI 0.67 to 1.26). However, indirect analyses should be interpreted with caution because they can give discrepant results compared to head-to-head comparisons.¹⁹²

In December 2004, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) was suspended in part because of an "apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo."¹¹¹ However, further details from the ADAPT trial have not yet become available.

Observational studies—naproxen. The risk of MI and other cardiovascular events associated with various non-selective NSAIDs has been evaluated in numerous observational studies. Naproxen has been the most extensively studied non-selective NSAID because of interest generated after the results of the VIGOR trial were published. In order to assess the proposed hypothesis that naproxen is protective against myocardial infarction (rather than rofecoxib causing additional myocardial infarctions), authors of a meta-analysis of randomized controlled trials of rofecoxib also analyzed 11 observational studies of naproxen (four based on the General Practice Research Database).¹²⁴ Compared with non-naproxen NSAIDs, naproxen was associated with a small cardioprotective effect (OR 0.86, 95% CI 0.75 to 0.99). The modest cardioprotective effect would not completely explain the 80% reduction in risk with naproxen compared with rofecoxib observed in the VIGOR trial. In addition, meta-regression analyses indicated that the funding source largely explained between-study heterogeneity. Specifically, Merck-funded studies of naproxen reported larger cardioprotective effects.

An FDA review of four observational studies of naproxen reporting a cardioprotective effect illustrate some difficulties in interpreting the results.¹⁴⁸ In a study by Rahme and colleagues, current exposure to naproxen was associated with a lower risk of acute MI compared with exposure to other NSAIDs (OR 0.79, 95% CI 0.63 to 0.99).¹⁹³ However, when the FDA reviewer re-analyzed the data to compare current exposure to naproxen to non-use of NSAIDs, naproxen was associated with a *higher* risk (OR 1.28, 95% CI 1.10 to 1.49).¹⁴⁸ Although the FDA re-analysis was not adjusted for confounders, examination of adjusted and unadjusted results in the paper suggests that the effects of adjusting would be minor. A study by Kimmel and colleagues found naproxen associated with a lower risk of MI compared with non-use (OR 0.48, 95% CI 0.28 to 0.82), but the results were susceptible to participation bias (about 50% of cases and controls participated) and recall bias (exposure determined by telephone interviews rather than by using pharmaceutical databases or other sources).¹⁹⁴ The third study, by Watson

and colleagues, reported a lower risk of thromboembolic cardiovascular events with current use of naproxen versus non-use (OR 0.61, 95% CI 0.39 to 0.94), but did not adequately control for baseline cardiovascular risk (it used an unvalidated composite measure of risk).¹⁹⁵ Further, when the endpoint of MI alone rather than the composite endpoint of thromboembolic cardiovascular events (which included subdural hematoma, subarachnoid hemorrhage, ischemic stroke, sudden death, or MI) was evaluated, the reduction in risk was not significant (OR 0.57, 95% CI 0.31 to 1.06). Finally, a study by Solomon and colleagues reported a lower risk of MI with use of naproxen within 6 months of an acute MI (OR 0.84, 95% CI 0.72 to 0.98).¹⁹⁶ However, the risk was reduced to a similar degree when the naproxen prescription had run out between 61 and 180 days earlier. Unless naproxen exerts a long-term cardioprotective effect (which is thought to be highly unlikely), these findings are suggestive of underlying selection bias—in other words, persons receiving naproxen were at lower risk for cardiovascular events, and adjustment for known confounders did not eliminate this bias.

In four other recent observational studies (not included in the Juni systematic review) evaluating cardiovascular risk, naproxen was not associated with a cardioprotective effect relative to non-use (Table 20).^{143, 146, 149, 155, 160} However, naproxen was also not clearly associated with an increased risk of myocardial infarction. None of these studies received pharmaceutical industry funding. The FDA review also included two other unpublished studies (Ingenix and MediCal studies) that found no cardioprotective benefit associated with naproxen.¹⁴⁸

Table 20. Risk of myocardial infarction associated with naproxen in recent observational studies not included in the Juni meta-analysis

Study	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴⁶	1.27 (1.01 to 1.60)
Levesque, 2005 ¹⁴³	1.17 (0.75 to 1.84)
Johnsen, 2005 ¹⁴⁹	1.50 (0.99 to 2.29)
Andersohn 2006 ¹⁵⁵	1.16 (0.86 to 1.58)

Overall, the general conclusion from observational studies of a modest decrease in cardiovascular risk associated with naproxen relative to other NSAIDs appears consistent with a systematic review of RCTs.¹²⁹ On the other hand, protective cardiovascular effects of naproxen relative to non-use observed in some observational studies usually appear to be explainable by issues related to study design or analysis. More recent, high-quality observational studies are mostly consistent with a neutral cardiovascular effect of naproxen relative to non-use.

Observational studies—non-naproxen NSAIDs. Results from observational studies regarding the cardiovascular risk associated with non-naproxen, non-selective NSAIDs are mixed. Non-selective NSAIDs as a class and individual NSAIDs have not been consistently associated with increased risks. Results from recent observational studies from the COX-2 era are summarized in Table 21.

Table 21. Risk of myocardial infarction associated with non-selective, non-naproxen NSAIDs

Study	Drug	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴⁶	Ibuprofen	1.24 (1.11 to 1.39)
	Diclofenac	1.55 (1.39 to 1.72)
	Other non-selective, non-naproxen NSAIDs	1.21 (1.02 to 1.44)
Graham, 2005 ¹⁶⁰	Non-selective, non-naproxen NSAIDs	1.13 (1.01 to 1.27)
Levesque, 2005 ¹⁴³	Non-selective, non-naproxen NSAIDs	1.00 (0.73 to 1.37)
Johnsen, 2005 ¹⁴⁹	Non-selective, non-naproxen NSAIDs	1.50 (0.99 to 2.29)
Garcia Rodriguez, 2004 ¹⁸⁵	Ibuprofen	1.06 (0.87 to 1.29)
	Diclofenac	1.18 (0.99 to 1.40)
	Ketoprofen	1.08 (0.59 to 1.96)
	Piroxicam	1.25 (0.69 to 2.25)
	Indomethacin	0.86 (0.56 to 1.32)
	Other non-selective, non-naproxen NSAIDs	0.89 (0.63 to 1.25)
Mamdani, 2003 ¹⁴⁷	Non-selective, non-naproxen NSAIDs	1.2 (0.9 to 1.4)
Ray, 2002 ¹⁵¹	Ibuprofen	0.91 (0.78 to 1.06)
Solomon, 2002 ¹⁹⁶	Ibuprofen	1.02 (0.88 to 1.18)
Watson, 2002 ¹⁹⁵	Ibuprofen	0.74 (0.35 to 1.55)
	Diclofenac	1.68 (1.14 to 2.49)
Andersohn, 2006 ¹⁵⁵	Ibuprofen	1.00 (0.83, 1.21)
	Diclofenac	1.36 (1.17, 1.58)
Schlienger 2002 ¹⁹⁷	Ibuprofen	1.17 (0.87, 1.58)
	Diclofenac	1.38 (1.08, 1.77)
	Piroxicam	1.65 (0.78, 3.49)
	Ketoprofen	1.39 (0.77, 2.51)
	Indomethacin	1.03 (0.58, 1.85)
	Flurbiprofen	2.26 (0.93, 5.46)

In April 2005, after reviewing the available observational data, the FDA issued a Public Health Advisory stating, “Long-term controlled clinical trials have not been conducted with most of these (non-selective) NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and non-selective NSAIDs with the data available. All sponsors of non-selective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk.”¹⁹⁸ The FDA also required labeling changes to both prescription and non-prescription non-selective NSAIDs warning about potential cardiovascular risks.

Aspirin. Aspirin is known to be protective against occlusive vascular events because of its irreversible antiplatelet effects. In a collaborative meta-analysis of 65 randomized controlled trials of aspirin for prophylaxis against thrombotic events, any dose of aspirin reduced the risk of vascular events by an average of 23% (standard error 2).¹⁹⁹ The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg/day, but in trials that directly compared higher and lower doses, there were no significant differences. Again, the populations evaluated in these trials probably varied substantially from trials of

patients with arthritis.

In fact, randomized controlled trials assessing the risk of upper GI bleeding with aspirin have mainly been conducted in populations receiving aspirin as prophylaxis for thrombotic events. It is for this reason that the populations evaluated in these trials may differ on risk factors for bleeding compared to patients who take aspirin for arthritis, as well as being at higher cardiovascular risk. Randomized controlled trials²⁰⁰ and observational studies generally reported that aspirin increases risk of serious GI events relative to placebo or non-use,^{138, 190, 200, 201} but at a rate similar to that of other non-selective NSAIDs.^{138, 189, 190} In these studies, the dose of aspirin varied widely and was generally lower (50 mg to 1500 mg daily) than the doses considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods. In a good-quality meta-analysis of 24 randomized trials with nearly 66,000 participants, the risk of gastrointestinal hemorrhage was 2.47% with aspirin compared with 1.42% with placebo (OR 1.68, 95% CI 1.51 to 1.88), based on an average of 28 months therapy.²⁰⁰ There was no relation between gastrointestinal hemorrhage and dose in this study. Further, modified release formulations did not attenuate the risk for bleeding. In a more recent, fair-quality meta-analysis of 31 randomized trials with over 190,000 subjects, the risk of major bleeding was 1.56% with doses <100 mg, 1.54% with 100-200 mg, and 2.29% with >200.²⁰² Although the difference between doses >200 and <100 was statistically significant, the absolute differences are small.

Systematic reviews of cohort and case-control studies published between 1985 and 2001 reported similar findings,^{189, 190, 201} except that the most recent review found a dose-response relationship between aspirin and risk of bleeding.¹⁸⁹ However, aspirin was associated with upper GI bleeding even at low doses. Findings from a recent UK practice-based case-control study (9,407 cases) found that compared with non-use, aspirin was associated with an increased risk of complicated or uncomplicated adverse GI events (odds ratio 1.60, 95% CI 1.49, 1.72) similar to that of naproxen, diclofenac, and ibuprofen.¹³⁸ These findings are consistent with a systematic review of observational studies that only assessed peptic ulcer-related hospitalizations.¹⁹⁰

Salsalate. Serious GI event rates (bleeding, perforation, obstruction) associated with salsalate were only reported in one cohort of long-term care residents in Indiana. The number of cases of GI-related hospitalizations associated with salsalate (1, 5.9%) after 14 months was similar to that of other selective and non-selective NSAIDs (cited in partially selective NSAID section above).¹⁸⁰

Other Adverse Events Associated with Selective and Non-Selective NSAIDs

Mortality. Large clinical trials have not shown differences in mortality rates between different NSAIDs. In VIGOR, for example, mortality was 0.5% with rofecoxib versus 0.4% with naproxen,¹⁹ and in CLASS mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.⁹⁴ A meta-analysis that included unpublished company clinical trial data (including CLASS) found no significant difference in rates of death in patients randomized to celecoxib compared with non-selective NSAIDs, though there were few events (0.03% or 6/18,325 in the celecoxib arms versus 0.11% or 14/12,685 in the NSAID arms).⁶² In one retrospective cohort study of Saskatchewan health-services databases that followed patients from 6 months following prescription until death, nabumetone was associated with significantly lower rates of all-cause mortality compared with diclofenac (adjusted odds ratio 1.96; 95% CI

1.25, 3.07) and naproxen (adjusted odds ratio 2.95, 95% CI 1.88, 4.62).²⁰³ However, we found no other studies replicating this finding.

Hypertension, CHF, edema, and renal function. All non-selective NSAIDs appear to be associated with increases in blood pressure. However, evidence regarding differential effects of specific NSAIDs is somewhat conflicting. Two meta-analyses of placebo-controlled trials have compared the effects of different non-selective NSAIDs on blood pressure increases.^{204, 205} One meta-analysis found that non-selective NSAIDs raised mean blood pressure by an average of about 5.0 mm Hg (95% CI, 95% CI 1.2 to 8.7).²⁰⁴ Piroxicam produced the most marked elevation in blood pressure.²⁰⁴ By contrast, the other meta-analysis found that piroxicam and ibuprofen had negligible effects on blood pressure, and that indomethacin and naproxen were associated with the largest increases.²⁰⁵ In both meta-analyses, aspirin and sulindac were associated with minimal hypertensive effect. In an analysis of head-to-head trials, there were no significant differences between indomethacin and sulindac (10 trials), indomethacin and salicylate (one trial), diclofenac and sulindac (one trial), ibuprofen and sulindac (one trial), and naproxen and sulindac (three trials).²⁰⁴ The reliability of the meta-analyses is compromised by a high likelihood of publication bias; more than half of published NSAID trials did not report hypertension rates as an outcome.²⁰⁵

Several studies have reported hypertension outcomes for selective COX-2 inhibitors compared to non-selective NSAIDs. One fair-quality meta-analysis found COX-2 inhibitors as a class (celecoxib, rofecoxib, and etoricoxib) not associated with an increased risk of developing hypertension compared to non-selective NSAIDs (RR 1.25, 95% CI 0.87 to 1.78). Pooling evidence on blood pressure effects from various selective and non-selective NSAIDs may be misleading, however, because of potential differences between COX-2 inhibitors, dissimilarities in dosing and comparator drugs, and a high likelihood of publication bias affecting conclusions.

Evidence regarding risks of hypertension with rofecoxib is somewhat mixed. A good-quality Cochrane review found that rates of edema and hypertension were not reported in most trials.⁷⁷ For rofecoxib versus nabumetone, there was no difference in the rate of hypertension in two trials (pooled RR 1.46, 95% CI 0.53 to 4.12). A meta-analysis of nine phase IIb/III osteoarthritis trials sponsored by the manufacturer of rofecoxib found that rofecoxib 12.5 mg and 25 mg daily were associated with higher rates of lower extremity edema, congestive heart failure, and hypertension than placebo.²⁰⁶ Edema and hypertension rates were similar between the rofecoxib (1.2 per 100 patient-months) and ibuprofen (1.3 per 100 patient-months) groups but somewhat higher than in the diclofenac group (0.3 per 100 patient months). Discontinuations due to these adverse events were rare: of 2,829 randomized to rofecoxib, seven discontinued due to edema, two due to hypertension, and one due to CHF. However, five of the nine trials were shorter than 6 weeks in duration, so these rates may not be representative of results in long-term users. A more recent fair-quality meta-analysis of arthritis trials found rofecoxib associated with a higher risk of developing hypertension compared to either placebo (RR 2.63, 95% CI 1.42 to 4.65) or non-selective NSAIDs (RR 1.78, 95% CI 1.17 to 2.69).²¹

Results of large, longer-term trials appear to be consistent with an increased risk of hypertension with rofecoxib compared to either placebo or non-selective NSAIDs. In VIGOR (N=8,076) rofecoxib 50 mg daily was associated with a higher risk of developing hypertension compared to naproxen (RR 1.69, 95% CI 1.42-1.99) and a higher risk of discontinuation due to hypertension-related adverse events (RR 4.67, 95% CI 1.93 to 11.28).¹¹⁴ In addition, 19 patients developed CHF-related adverse events during 4,047 patient-years of exposure, compared with

nine patients during 4,029 patient-years of exposure to naproxen (RR 2.11, 95% CI 0.96 to 4.67). In the long-term APPROVe polyp prevention trial, hypertension (RR 2.02, 95% CI 1.71 to 2.38), edema (RR 1.57, 95% CI 1.17 to 2.10), and heart failure or pulmonary edema (RR 4.61, 95% CI 1.50 to 18.83) were all increased with rofecoxib 25 mg qD compared with placebo.¹³²

In contrast to rofecoxib, several meta-analyses of celecoxib suggest no increased risk of hypertension or heart failure compared to non-selective NSAIDs. In fact, a recent fair-quality meta-analysis found celecoxib (dose not specified) not associated with an increased risk of hypertension compared to either placebo (RR 0.81, 95% CI 0.13 to 5.21) or non-selective NSAIDs (RR 0.82, 95% CI 0.68 to 1.00).²¹ On the other hand, a Pfizer-funded meta-analysis submitted to the FDA found that, for celecoxib (any dose), the risk of developing hypertension was higher than placebo (1.1% vs. 0.7%, $p=0.023$) but lower than the non-selective NSAIDs (1.5% vs. 2.0%, $p=0.002$).¹³⁵ Heart failure was more frequent in patients taking celecoxib than those taking placebo (13 of 8,405 versus one of 4,057, $p=0.046$), though not compared with non-selective NSAIDs (0.1% vs. 0.2%, $p=0.056$). A third meta-analysis, funded in part by the manufacturer, reported similar findings for risk of hypertension (celecoxib vs. non-selective NSAID RR 1.1, 95% CI 0.90 to 1.3) and heart failure (celecoxib vs. non-selective NSAID RR 0.70, 95% CI 0.43 to 1.1).⁶² Most of the trials included in the meta-analyses were short-term and only one meta-analysis⁶² evaluated the quality of the trials. However, results from large trials of celecoxib are consistent with the meta-analyses. In CLASS (N=8,059), celecoxib was associated with a similar rate of hypertension (new-onset and aggravated pre-existing) compared with diclofenac (2.7% vs. 2.6%), but a significantly lower rate than ibuprofen (2.7% vs. 4.2%).¹⁰⁵ CHF rates were similar in patients randomized to celecoxib versus either ibuprofen or diclofenac (0.3% vs. 0.3%). In the shorter-term SUCCESS-I trial (N=13,274), rates of hypertension were similar with celecoxib 100 or 200 mg bid compared to either diclofenac or naproxen (RR 0.86, 95% CI 0.62 to 1.20).²¹ The APC polyp prevention trial found celecoxib associated with significant systolic blood pressure elevations compared to placebo at 1 and 3 years at either 200 mg twice daily (2.0 mm Hg at 1 year and 2.6 mm Hg at 3 years) and 400 mg twice daily (2.9 mm Hg at 1 year and 5.2 mm Hg at 3 years).¹⁰⁹ By contrast, the PreSAP polyp prevention trial found no difference in systolic blood pressure elevations between celecoxib 400 mg once daily and placebo.¹⁰⁹ The APC polyp prevention trial found no difference in rates of heart failure between patients randomized to celecoxib versus those randomized to placebo, though event rates were low (five cases of heart failure among 1,356 subjects).¹⁰⁸

Direct evidence on comparative blood pressure effects of celecoxib compared to rofecoxib is more limited. A good-quality Cochrane review found no difference in rates of clinically significant increases in blood pressure or edema with rofecoxib versus celecoxib in three head-to-head trials of average-risk populations with osteoarthritis.⁷⁷ Another meta-analysis that used unpublished clinical trial reports also found no difference in risk of hypertension or aggravated hypertension in patients on celecoxib versus rofecoxib (RR 0.75, 95% CI 0.52 to 1.1).⁶² On the other hand, in contrast to the Cochrane review, this meta-analysis found a lower rate of edema with celecoxib versus rofecoxib (5 trials, RR 0.72, 95% CI 0.62 to 0.83). A third meta-analysis found rofecoxib associated with a greater risk of developing a clinically important elevation in systolic blood pressure (RR 1.50, 95% CI 1.00 to 2.26), though the difference was not statistically significant.²¹

Three other short-term head-to-head trials of celecoxib and rofecoxib in higher-risk populations (hypertensive, osteoarthritic patients) funded by the manufacturer of celecoxib should be interpreted cautiously because they evaluated doses (rofecoxib 25 mg daily and

celecoxib 200 mg daily) that may not provide equivalent pain relief.^{84, 85, 207} Two 6-week trials of elderly (>65 years) patients with osteoarthritis and on antihypertensive therapy (SUCCESS VI and SUCCESS VII) found that rates of increased systolic blood pressure (>20 mm Hg increase and absolute value >140 mm Hg) were higher in patients randomized to rofecoxib (n=399) compared to celecoxib (n=411): 14.9% vs. 6.9% ($p<0.01$) in one trial⁸⁵ and 17% vs. 11% ($p=0.032$) in the other.⁸⁴ However, in one of these trials (SUCCESS VI),⁸⁴ there was an important baseline difference in the proportion of patients who took an ACE inhibitor for hypertension (40% for celecoxib-treated patients versus 29% for rofecoxib-treated patients, $p=0.002$). This could suggest inadequate randomization, as successful randomization is unlikely to have resulted in such a marked baseline difference. In the third trial (CRESCENT), which enrolled patients with controlled hypertension, diabetes, and osteoarthritis, the proportion that developed ambulatory hypertension (systolic blood pressure >135) was higher with rofecoxib than with celecoxib (30% vs. 16%, $p=0.05$).²⁰⁷ In the CRESCENT and SUCCESS-VI trials, edema was more common in patients assigned to rofecoxib compared with those assigned to celecoxib (7.7% vs. 4.7%, $p<0.05$ ²⁰⁷ and 9.5% vs. 4.9%, $p=0.014$ ⁸⁴). Three patients on rofecoxib and two on celecoxib developed heart failure in CRESCENT compared with four versus none in SUCCESS-VI; these differences were not significant. Discontinuations due to these adverse events did not differ.

With regards to renal toxicity, there is little evidence to suggest that selective NSAIDs as a class are safer than non-selective NSAIDs. A systematic review of five small (sample size range 15 to 67), short-term (28 days or less) trials found that selective NSAIDs had similar effects on glomerular filtration rate and creatinine clearance in three trials, and were modestly superior in two.²⁰⁸ The clinical effects of the modest differences observed in the latter two trials are unclear. Another meta-analysis found that celecoxib at 200 to 400 mg was not associated with a greater risk of increase in creatinine greater than 1.3 times the upper limit of normal compared to non-selective NSAIDs (RR 0.78, 95% CI 0.46 to 1.3).⁶²

There is also no clear evidence suggesting that celecoxib is associated with improved renal safety compared with rofecoxib. In the CLASS trial, there was one fewer episode of edema, hypertension, or increased creatinine for every 62 patients treated with celecoxib instead of ibuprofen 800 mg tid or diclofenac 75 bid.⁶⁰ The effects of celecoxib on renal function were also reviewed in a meta-analysis of primarily unpublished data (not including CLASS) that found the overall incidence of renal adverse events similar to that of non-selective NSAIDs.²⁰⁹ In VIGOR, the incidence of adverse events related to renal function (outcome not specifically defined) was similar for the rofecoxib and naproxen groups (1.2% versus 0.9%), with 0.2% discontinuing treatment in each arm because of these events.¹⁹ A meta-analysis of manufacturer's data found rofecoxib associated with an overall incidence of elevations in serum creatinine similar to non-selective NSAIDs.²⁰⁶ Discontinuations due to elevated serum creatinine were rare, and there were no cases of acute renal failure (not defined) associated with rofecoxib.

The risks of hypertension and heart failure with rofecoxib and celecoxib have also been evaluated in several good-quality observational studies. A large case-control study found that rofecoxib users were at significantly increased risk for new-onset hypertension compared with patients taking celecoxib (OR 1.6, 95% CI 1.2 to 2.1).²¹⁰ A retrospective cohort study found rofecoxib associated with an increased risk of admission for heart failure compared with NSAID-non-users (RR 1.8, 95% CI 1.5 to 2.2), though celecoxib was not (RR 1.0, 95% CI 0.8 to 1.3).¹⁶³ Rofecoxib (HR 1.27, 95% CI 1.09 to 1.49) and non-selective NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) were also associated with higher risks of death or recurrent CHF compared with

celecoxib in another study of high-risk patients following a heart-failure admission.²¹¹ In two observational studies, use of non-selective NSAIDs was associated with heart-failure admissions (RR 1.4, 95% CI 1.0 to 1.9)¹⁶³ and newly diagnosed heart failure (adjusted RR 1.6, 95% CI 1.2 to 2.1)²¹² when compared with non-use.

Hepatotoxicity. We identified one systematic review that evaluated rates of aminotransferase elevations, liver-related discontinuations, and other serious hepatic adverse events, including hospitalizations and deaths, in randomized controlled trials of rofecoxib, celecoxib, valdecoxib, meloxicam, diclofenac, naproxen, and ibuprofen in adults with osteoarthritis or rheumatoid arthritis.²¹³ It identified 67 published articles and 65 studies accessible from the FDA archives. Diclofenac (3.55%, 95% CI 3.12% to 4.03%) and rofecoxib (1.80%, 95% CI 1.52% to 2.13%) had higher rates of aminotransferase elevations >3 times the upper limit of normal compared with placebo (0.29%; 95% CI 0.17% to 0.51%) and the other NSAIDs (all < or = 0.43%). However, only diclofenac was associated with a higher rate of liver-related discontinuations than placebo (2.17%, 95% CI 1.78% to 2.64%). Serious complications related to liver toxicity were extremely rare: only one liver-related hospitalization (among 37,671 patients) and death (among 51,942 patients) occurred in a patient on naproxen in the VIGOR trial. There was also a statistically significant difference in elevated (three times above the upper limit of normal) transaminase levels between lumiracoxib (which is chemically related to diclofenac) and naproxen or ibuprofen (HR 3.97, 95% CI 2.96, 5.32) in the large TARGET (N=18,325) trial, though these elevations were reversible upon drug discontinuation.¹⁷⁵

A recent systematic review of seven population-based epidemiological studies of hepatotoxicity with NSAIDs found a similarly low risk of serious hepatic toxicity.²¹⁴ In those studies, the excess risk of liver injury associated with current NSAIDs ranged from 4.8 to 8.6/100,000 person-years of exposure compared with past use. There were zero deaths from liver injury associated with NSAIDs in over 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the U.S., was associated with a higher incidence of serious liver injury compared with other NSAIDs.²¹⁵ None of the other NSAIDs, including celecoxib, were associated with an increased risk of serious liver injury. An earlier review of five population-based studies found sulindac associated with a 5-10 fold higher incidence of hepatic injury compared with other NSAIDs.²¹⁶ Diclofenac was associated with higher rates of aminotransferase elevations compared with users of other NSAIDs, but not with a higher incidence of serious liver disease.

Tolerability: Comparison of NSAIDs

Partially selective NSAIDs. Evidence is mixed regarding the relative tolerability of meloxicam (7.5 mg or 15 mg) compared to non-selective NSAIDs. The meta-analysis of meloxicam studies mentioned earlier found lower rates of any gastrointestinal event (OR 0.64; 95% CI 0.59, 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52, 0.67) compared with NSAIDs, but as mentioned before it included some inadequately blinded studies, which are less reliable for assessing withdrawals and attributing the cause of adverse events.¹⁸¹ The double-blind trial of meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid mentioned earlier²¹⁷ found no significant differences in rates of withdrawals due to adverse events or in incidence of overall and gastrointestinal tolerability.

In the nabumetone meta-analysis, the incidence of GI adverse events was significantly lower on nabumetone compared to non-selective NSAIDs (25.3% vs. 28.2%, p=.007), corresponding to

about one fewer event for every 34 patients treated with nabumetone.¹⁸⁷

Numerous randomized controlled trials reported microscopic bleeding or endoscopic outcomes with etodolac. However, we identified no randomized trials or systematic reviews assessing the clinical tolerability of etodolac relative to non-selective NSAIDs.

Non-selective NSAIDs. One Cochrane review evaluated the tolerability of different NSAIDs.⁴¹ The only relatively consistent finding was that indomethacin was associated with higher rates of toxicity than other NSAIDs, but it was not clear if these differences were statistically significant.

Aspirin and salsalate. Five randomized trials have evaluated the efficacy or safety of aspirin or salsalate compared with non-aspirin NSAIDs in patients with arthritis.^{56, 218-221} All were short-term in duration (≤ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only four had osteoarthritis of the hip/knee for every 100 patients with rheumatoid arthritis. Aspirin was associated with higher incidence of overall adverse events than salsalate (70% vs. 40%, $p < 0.05$)⁵⁶ and diclofenac (61% vs. 46%; $p < 0.05$);²¹⁸ these led to higher rates of withdrawals due to adverse events for aspirin compared with diclofenac (23% vs. 6%; $p < 0.05$). Salsalate was associated with a higher incidence of overall adverse events compared to other non-selective NSAIDs in two^{220, 221} of three trials, but the actual rates were not reported.

The overall safety profile of salsalate has also been evaluated in the rheumatoid arthritis population using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) databases. These studies reported summary measures of drug toxicity based on tabulations of mean frequencies of overall adverse events per patient years, weighted by severity, and adjusted for differences in demographic factors. Numerically larger index scores indicate greater levels of toxicity. The summary index score takes into account symptoms from all body systems, laboratory abnormalities, and all-cause hospitalizations.^{201, 222-224} Symptoms were assessed every 6 months using patient self-report in response to open-ended questions. Hospitalization and death data were ascertained from discharge summaries and death certificates. Descriptions of study methods varied, but in general the ARAMIS studies were somewhat vague with regard to patient selection and ascertainment methods; adverse events were not clearly defined or prespecified; exposure duration and length of follow-up were unclear; and adjustments were made only for demographic factors such as age and gender. Because the results of these studies are more subject to recall bias and had other methodological shortcomings, the findings that aspirin, salsalate, and ibuprofen were the least toxic among the NSAIDs studied (Table 22 below) are less convincing than results of more recent observational studies (discussed earlier).

Table 22. Toxicity Index Scores from ARAMIS database studies

Study	Aspirin	Ibuprofen	Salsalate	Others (range)
Fries 1991 ²²²	1.19	1.94	1.28	2.17 (Naproxen) to 3.99 (Indomethacin)
Fries 1993 ²²⁴	1.33	1.89	NR	1.90 (Naproxen) to 2.86 (Tolmetin)
Fries 1996 ²²³	1.77	2.68	2.00	1.63 (Sulindac) to 3.09 (Ketoprofen)
Singh 1997 ²⁰¹	2.25	1.95	1.79	3.29 (Naproxen) to 5.14 (Meclofenamate)

COX-2 vs. NSAID. Two manufacturer-funded meta-analyses^{61, 62} and one good-quality Cochrane review²²⁵ found celecoxib consistently associated with more favorable overall and GI tolerability profiles relative to some, but not all, non-selective NSAIDs in short-term RCTs of

patients with OA/RA (Table 23). Evidence of relative tolerability is less consistent for rofecoxib compared to partially-selective or non-selective NSAIDs in short-term RCTs of patients with OA/RA as reported in one manufacturer-funded meta-analysis,²²⁶ two good-quality Cochrane reviews,^{77, 78} and one other RCT that was not included in the systematic reviews.⁷⁶

Effect size differences between the COX-2 manufacturer-funded analyses and the Cochrane reviews may have been due, in large part, to differences in methods of study selection and statistical analyses. The Cochrane Reviews primarily relied upon electronic database searches for identification of published RCTs evaluating narrow patient populations, and results from each trial were generally presented separately.^{77, 78, 225} Manufacturer-funded meta-analyses relied solely^{62, 226} or in part⁶¹ on internal records to identify studies and presented only pooled estimates of broader populations including OA and RA patients.

Table 23. Tolerability profile of COX-2's vs. NSAIDs in meta-analysis and systematic reviews

Review	AE Incidence		Withdrawals	
	Overall	GI-related	Any AE	GI-related
Celecoxib vs. NSAIDs for OA/RA				
<i>Manufacturer-funded meta-analyses</i>				
Deeks 2002 ⁶¹	-	-	RR 0.86 (0.72, 1.04)	RR 0.54 (0.42, 0.71)
Moore 2005 ⁶²	0.96 (0.94, 0.98)	0.84 (0.81, 0.87)	RR 0.86 (0.81, 0.91)	RR 0.75 (0.7, 0.8)
Celecoxib vs. individual NSAIDs for RA				
<i>Gamer 2005a²²⁵ (Cochrane Collaboration Systematic Review)</i>				
<i>Celecoxib vs. Naproxen</i>				
-	-	-	No differences (RR Range: 1.02-1.36)	No differences (RR Range: 0.26-0.61)
<i>Celecoxib vs. Diclofenac</i>				
-	0.75 (0.62, 0.90)	0.95 (0.85, 1.04)	0.54 (0.36, 0.79)	0.36 (0.21, 0.60)
Rofecoxib vs. NSAIDs for OA				
<i>Watson 2000²²⁶ (Manufacturer-funded meta-analysis)</i>				
6-month	-	0.86 (0.78, 0.95)	-	0.68 (0.50, 0.92)
12-month	-	0.88 (0.80, 0.97)	-	0.70 (0.52, 0.94)
<i>Gamer 2005c⁷⁷ (Cochrane Collaboration Systematic Review)</i>				
<i>Rofecoxib vs. Diclofenac</i>				
No differences (RR range: 0.98-1.01)	-	-	12.5 mg: 0.71 (0.52, 0.97) 25 mg: 0.70 (0.51, 0.95)	-
<i>Rofecoxib vs. Ibuprofen</i>				
NS (RR range: 0.98-1.04)	-	-	↓ risk in 2 of 3 RCTs	No differences in 3 of 4 RCTs
<i>Rofecoxib vs. Naproxen</i>				
No differences	0.55 (0.42, 0.73)	-	No differences	↓ risk in 2 of 3 RCTs
<i>Rofecoxib vs. Nabumetone</i>				
NR	NR	-	No differences	No differences
Rofecoxib vs. Naproxen in RA				
<i>Gamer 2005b⁷⁸ (Cochrane Collaboration Systematic Review)</i>				
-	-	-	1.02 (0.92, 1.12)	0.74 (0.64, 0.85)

A manufacturer-funded meta-analysis found that tolerability of valdecoxib relative to NSAIDs appeared to be time-dependent.²²⁷ Significant increases in overall adverse event incidence (RR 1.1; 95% CI 1.04, 1.2) and incidence of GI adverse events (RR 1.4; 95% CI 1.2, 1.6) for valdecoxib relative to NSAIDs did not lead to increased risk of discontinuation in RCTs

of 6-12 weeks' duration. By 12-26 weeks, however, valdecoxib was associated with significantly lower rates of overall adverse events (RR 0.9; 95% CI 0.85, 0.93) and GI-related adverse events (RR 0.7; 95% CI 0.7, 0.8) relative to non-selective NSAIDs, as well as lower rates of discontinuation due to any adverse event (RR 0.9; 95% CI 0.85, 0.93) and due to GI-related adverse events (RR 1.4; 95% CI 1.2, 1.6).

Comparison between COX-2 inhibitors. Incidence of and withdrawals due to overall or GI-related adverse events were similar for celecoxib and rofecoxib across a manufacturer-funded meta-analysis⁶² and a good-quality Cochrane review.⁷⁷ The manufacturer-funded meta-analysis reported that rofecoxib and celecoxib were associated with similar risks of any adverse event (RR 0.97; 95% CI 0.84, 1.1), any GI-related adverse event (RR 0.87, 95% CI 0.74, 1.03), and GI-adverse event discontinuation (RR 0.7; 95% CI 0.5, 1.2) using data from five 6- to 12-week RCTs of patients with either OA or RA.⁶² The Cochrane review of rofecoxib for osteoarthritis⁷⁷ found no differences for either the total number of withdrawals (RR 0.93, 95% CI 0.76 to 1.14) or the number of withdrawals due to adverse events (RR 1.03, 95% CI 0.77 to 1.39) in five trials that compared celecoxib to rofecoxib.

Acetaminophen. We identified four systematic reviews that evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or non-selective) for osteoarthritis.²²⁸⁻²³¹ The studies generally met all criteria for good-quality systematic reviews, except that three²²⁹⁻²³¹ did not provide sufficient detail about trials that were excluded. The overall conclusion from the reviews was that NSAIDs are modestly superior to acetaminophen for general or rest pain (Table 24). For pain on motion and overall assessment of clinical response, NSAIDs also appeared modestly superior, though the differences were not always statistically significant.^{229, 230} Only two reviews assessed functional disability; neither found clear differences.^{229, 230}

Table 24. Pain relief in systematic reviews of acetaminophen versus NSAID

Systematic review	Date of last search	Number of head-to-head trials included	Main results for outcome of general or rest pain
Towheed, 2005 ²²⁹	Through 8/02	5 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (SMD 0.32, 95% CI 0.08 to 0.56) and HAQ pain (SMD 0.27, 95% CI 0.05 to 0.48)
Zhang, 2004 ²³¹	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDs superior using WOMAC scale (pooled ES 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)
Lee, 2004 ²²⁸	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference -6.33, 95% CI -9.24 to -3.41)
Wegman, 2004 ²³⁰	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (standardized mean difference 0.33, 95% CI 0.15 to 0.51)

The risk of adverse events with acetaminophen versus NSAIDs was assessed in three systematic reviews (Table 25).^{228, 229, 231} In two reviews, there were no differences in withdrawal due to any adverse event.^{229, 231} However, acetaminophen was associated with fewer gastrointestinal side effects compared with non-selective NSAIDs (though not compared with coxibs)^{229, 231} and fewer withdrawals due to gastrointestinal adverse events.²²⁹

Table 25. Adverse events in systematic reviews of acetaminophen versus NSAID

Systematic review	Withdrawal due to adverse events	GI adverse events
Towheed, 2005 ²²⁹	No difference (8% vs. 9%)	Withdrawal due to GI adverse event Naproxen or ibuprofen vs. acetaminophen: RR 2.15 (95% CI 1.05 to 4.42) Any GI adverse event Non-selective NSAID vs. acetaminophen: RR 2.24 (95% CI 1.23 to 4.08) Coxib vs. acetaminophen: RR 0.96 (95% CI 0.57 to 1.61)
Zhang, 2004 ²³¹	Not reported	GI discomfort Non-selective NSAID vs. acetaminophen: RR 1.39 (95% CI 1.07 to 1.80) Coxib vs. acetaminophen: RR 0.65 (95% CI 0.17 to 2.52)
Lee, 2004 ²²⁸	NSAID vs. acetaminophen: OR 1.45, 95% CI 0.93 to 2.27)	Not reported

Results of recent, good-quality randomized trials (not included in any of the systematic reviews) were consistent with the systematic reviews. One two-week trial (N=222) found ibuprofen 1,200 mg/day more effective than paracetamol 3,000 mg/day for pain relief ($p<0.005$) and functional disability using WOMAC scores (-20.8 versus -13.4, $p<0.001$).²³² Two cross-over trials of identical design (N=524 and 556) found celecoxib modestly superior to acetaminophen for WOMAC scores (difference in WOMAC score improvements ranged from 2.8 to 5.0 points on a 100-point scale), visual analogue pain scales (mean difference in scores ranged from 3.5 to 7.7 mm on a 100 mm scale), and patient preferences (53% and 50% favored celecoxib, versus 24% and 32% favored acetaminophen).²³³ In all three trials, tolerability and safety were equivalent.

Clinical trials of acetaminophen have not been large enough to assess serious but less common complications such as PUB, myocardial infarction, acute renal failure, or hypertension. However, observational studies provide some additional information about the safety of acetaminophen relative to NSAIDs. A good-quality nested case-control study of 1,197 cases and 10,000 controls from a population-based cohort of 458,840 persons in the General Practice Research Database found current acetaminophen use associated with a lower risk for symptomatic peptic ulcer (adjusted RR 1.9, 95% CI 1.5 to 2.3) than NSAID use (adjusted RR 4.0, 95% CI 3.2 to 5.1) when each was compared with non-use.²³⁴ There was no clear relationship between higher acetaminophen dose and increased risk for symptomatic ulcers. An earlier analysis on the same database also found current acetaminophen use associated with a lower risk for upper gastrointestinal bleeds or perforations (adjusted RR 1.3, 95% CI 1.1 to 1.5) than current NSAID use (adjusted OR 3.9, 95% CI 3.4 to 4.6), each compared with non-use.¹⁸⁴ A retrospective cohort study of elderly patients found that patients using lower doses of acetaminophen (<2,600 mg/day) had lower rates of GI events (defined as GI-related hospitalizations, ulcers, and dyspepsia) compared with users of NSAIDs (RR 0.73, 95% CI 0.67 to 0.80 for 1,951 to 2,600 mg/day), but the risks were similar at higher doses (RR 0.93 to 0.98).²³⁵ Although GI hospitalization rates were not reported separately, the authors noted that dyspepsia was responsible for most of the increase in GI events in the high-dose acetaminophen groups. A meta-analysis on individual patient data from three earlier retrospective case-control studies (2472 cases) was consistent with the above studies.²³⁶ It found acetaminophen associated

with a minimal increase in the risk for serious upper gastrointestinal bleeding (OR 1.2, 95% CI 1.1 to 1.5). By contrast, non-selective NSAIDs were associated with higher risks, though estimates of risk varied considerably for different NSAIDs (OR 1.7 for ibuprofen to 34.9 for ketoprofen).

No randomized trial has evaluated the association between acetaminophen use and myocardial infarction or other thromboembolic cardiovascular events. However, a recent analysis from the large, prospective Nurses' Health Study found heavy use of acetaminophen (more than 22 days/month) associated with an increased risk of cardiovascular events (RR 1.35, 95% CI 1.14 to 1.59) similar to that with heavy use of NSAIDs (RR 1.44, 95% CI 1.27 to 1.65).²³⁷ Dose- and frequency-dependent effects were both significant.

The association between renal failure and acetaminophen use has been evaluated in several case-control studies. Interpretation of these studies, however, is difficult because many had important flaws (such as failure to identify patients early enough in the course of their disease to insure that the disease had not led to a change in the use of analgesics, failure to specify diagnostic criteria, failure to adjust for the use of other analgesics, incompleteness of data on exposure, and use of proxy respondents) in the collection or analysis of data.²³⁸ The largest (926 cases) case-control study was designed to try to avoid many of these flaws.²³⁹ It found regular use of acetaminophen associated with an increased risk for chronic renal failure (Cr >3.8 for men and >3.2 for women) compared with non-use (OR 2.5, 95% CI 1.7 to 3.6). Use of NSAIDs was not associated with an increased risk (OR 1.0). A prospective cohort study of 1,697 women in the Nurses' Health Study found increased lifetime acetaminophen exposure associated with a higher risk of decline in glomerular filtration rate of 30% or greater ($p < 0.001$), though NSAIDs were not ($p = 0.88$).²⁴⁰ The absolute risk of renal function decline, however, was modest, even in women reporting high amounts of lifetime acetaminophen use. Compared with women consuming less than 100 g of cumulative acetaminophen, the odds of a decline in GFR of at least 30 mL/min per 1.73 m² for women consuming more than 3,000 g was 2.04 (95% CI, 1.28 to 3.24). By contrast, analyses of men in the Physicians' Health Study found no association between acetaminophen or NSAIDs and change in kidney function.^{241, 242}

The risk of heart failure associated with acetaminophen has not been well studied. In a single study using the General Practice Research Database, current use of acetaminophen was associated with a higher risk of newly diagnosed heart failure compared with non-use (RR 1.33, 95% CI 1.06 to 1.67), though the risk was lower compared with current use of NSAIDs (RR 1.59, 95% CI 1.23 to 2.05).²¹²

The risk of hypertension has been evaluated using data from the Nurses' Health Studies²⁴³⁻²⁴⁵ and the Physicians' Health Study.²⁴⁶ In the Nurses' Health Studies, acetaminophen and NSAIDs were associated with similar increases in risk of incident hypertension (Table 26). In the Physicians' Health Study, on the other hand, there was no association between NSAID or acetaminophen use and hypertension.

Table 26. Incidence of hypertension in the Nurses' Health Study and Physicians' Health Study according to use of acetaminophen or NSAIDs

Study	Acetaminophen use versus non-use: odds ratio	NSAID use versus non-use: odds ratio
Nurses' Health Study I (women 51 to 77 years old) ²⁴³	1.93 (1.30 to 2.88)	1.78 (1.21 to 2.61)
Nurses' Health Study II (women 34 to 53 years old) ²⁴³	1.99 (1.39 to 2.85)	1.60 (1.10 to 2.32)
Physicians' Health Study ²⁴⁵	1.08 (95% CI 0.87 to 1.34)	1.05 (95% CI 0.89 to 1.24)

Although overdoses with acetaminophen can lead to potentially life-threatening hepatotoxicity, it is not clear if hepatotoxicity is associated with therapeutic doses in patients without underlying liver disease.¹⁶ We identified no studies comparing the incidence of hepatotoxicity with therapeutic doses of acetaminophen and NSAIDs. We also identified no studies comparing the incidence of myocardial infarctions in persons using acetaminophen compared with NSAIDs.

Glucosamine and Chondroitin

Data regarding the comparative efficacy of glucosamine versus NSAIDs in patients with osteoarthritis are mixed. The most promising results have been observed in trials sponsored by Rotta Research Laboratories (based in Europe), which manufactures pharmaceutical grade glucosamine not available in the U.S. Because the content and purity of over-the-counter glucosamine preparations vary substantially, the results of the Rotta trials may not be directly applicable in the U.S.²⁴⁷

A recently updated (searches through November 2004), good-quality Cochrane review included four short-term (4 to 8 weeks) head-to-head trials of glucosamine versus an oral NSAID (ibuprofen or piroxicam).²⁴⁸ Two of the trials were rated 5 out of 5 on the Jadad scale, and the other two were rated 3 or 4 out of 5. Rotta Research Laboratories sponsored three of the trials; the fourth²⁴⁹ was also conducted in Europe, but funding information was not reported. One of the trials has only been published as an abstract,²⁵⁰ and analyses were based on data from an unpublished manuscript. Two of the four trials found glucosamine superior to oral NSAIDs for efficacy,^{249, 250} and two found no difference.^{251, 252} In pooled analyses, glucosamine was superior to an oral NSAID for improving pain (three trials, standardized mean difference -0.40, 95% CI -0.60 to -0.19), but not for improving function using the Lequesne Index (two trials, SMD -0.36, 95% CI -1.07 to 0.35). Glucosamine was also associated with fewer adverse events (RR 0.29, 95% CI 0.19 to 0.44) and withdrawals due to toxicity (RR 0.06, 95% CI 0.01 to 0.25). Two small (N=40 and N=45), 12-week Canadian trials, neither funded by Rotta Research Laboratories, have also recently been published. Neither found differences between glucosamine and ibuprofen for general osteoarthritis pain²⁵³ or for temporomandibular joint osteoarthritis.²⁵⁴ Only limited details of the study design were reported for the first trial, though the second met all criteria for a good-quality study.

Evidence regarding the efficacy of glucosamine compared with placebo has also been mixed. The Cochrane review found glucosamine no better than placebo when the analysis was restricted to the eight trials with adequate allocation concealment.²⁴⁸ By contrast, when all placebo-

controlled trials were included in the analysis, glucosamine was superior for both pain and function using the Lequesne index. The benefits of glucosamine also varied substantially depending on the preparation being studied. Specifically, glucosamine performed better in the seven trials evaluating the Rotta preparation (a prescription formulation available in Europe) (SMD -1.31, 95% CI -1.99 to -0.64) compared with the eight trials using non-Rotta preparations (SMD -0.15, 95% CI -0.35 to 0.05). In fact, all of the five trials that found no benefit from glucosamine evaluated a non-Rotta brand of glucosamine and also had limited or no affiliation with a manufacturer of glucosamine. Older systematic reviews found glucosamine superior to placebo, but did not include several newer and higher quality trials that demonstrated no effect, and also noted important methodological flaws that could have exaggerated estimates of effect.^{255, 256} The Cochrane review²⁴⁸ and one other recent, good-quality systematic review²⁵⁷ included two trials (one fair-quality and one good-quality) that found glucosamine (Rotta brand) superior to placebo for reducing progression of knee joint space narrowing over 3 years (SMD 0.24, 95% CI 0.04 to 0.43²⁴⁸ and RR 0.46, 95% CI 0.28 to 0.73²⁵⁷). Other trials were too short in duration (mean 9 weeks) to assess joint space narrowing as an outcome. In all of the systematic reviews, rates of adverse events were no different between glucosamine and placebo.

We identified no trials comparing chondroitin sulfate to oral NSAIDs. Three systematic reviews evaluated the efficacy and safety of chondroitin compared with placebo. The most recent, fair-quality systematic review found indistinguishable efficacy for glucosamine and chondroitin and combined the results of the trials.²⁵⁶ When all trials were pooled, active treatment was associated with an increased likelihood of being a responder (RR 1.59, 95% CI 1.39 to 1.83) compared with placebo. The results of the chondroitin trials were not reported separately. The chondroitin trials also received lower quality ratings than the glucosamine trials, but the effects of quality scores on the findings were not evaluated. Assessment of the effects of quality on assessments of estimates of benefit are important because an earlier, good-quality systematic review found pooled effect sizes for pain relief substantially lower for chondroitin trials with quality scores below the median (effect size 1.7, 95% CI 0.7 to 2.7) compared with trials with quality scores above the median (ES 0.8, 95% CI 0.6 to 1.0).²⁵⁵ Smaller chondroitin trials also reported higher effects. The third systematic review was also rated fair quality because it did not evaluate the effects of study quality on results.²⁵⁸ It found chondroitin superior to placebo for pain and function, but longer and larger studies were needed. All three systematic reviews found chondroitin tolerated as well as placebo, with only mild adverse events.

Results of a large (N=1,583), NIH-funded, randomized trial (Glucosamine/chondroitin Arthritis Intervention Trial) comparing placebo, celecoxib, glucosamine, chondroitin, and glucosamine plus chondroitin were recently published (Table 27).²⁵⁹ Using pharmaceutical grade glucosamine hydrochloride (rather than the over-the-counter glucosamine sulfate commonly available in U.S. as supplements not regulated as pharmaceuticals by the FDA) and chondroitin under an investigational new drug application, the study randomized patients stratified according to baseline pain severity. It found no differences between glucosamine, chondroitin, or the combination relative to placebo among all patients for achieving a clinical response (>20% improvement in WOMAC Pain score after 24 weeks), though the combination was superior to placebo for achieving a clinical response in an analysis of a small (20% of enrollees) subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, p=0.002). There were no statistically significant differences between celecoxib and any of the other active treatment arms (glucosamine alone, chondroitin alone, or glucosamine plus chondroitin) or placebo and either glucosamine or chondroitin alone. The

authors postulated that lack of effect in the mild baseline pain group could have been due in part to floor effects. High placebo response rates were also observed. All of the interventions were well tolerated.

Table 27. Response rates in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)
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Intervention	All patients	Moderate-severe baseline pain (WOMAC pain score 301-400 mm)	Mild baseline pain (WOMAC pain score 125-300)
Placebo	60.1%	54.3%	61.7%
Celecoxib	70.1% (p=0.008 vs. placebo)	69.4% (p=0.06 vs. placebo)	70.3% (p=0.04 vs. placebo)
Glucosamine	64.0% (p=0.30 vs. placebo)	65.7% (p=0.17 vs. placebo)	63.6% (p=0.67 vs. placebo)
Chondroitin	65.4% (p=0.17 vs. placebo)	61.4% (p=0.39 vs. placebo)	66.5% (p=0.27 vs. placebo)
Glucosamine + chondroitin	66.6% (p=0.09 vs. placebo)	79.2% (p=0.002 vs. placebo)	62.9% (p=0.80 vs. placebo)

Key Question 1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?

Duration of exposure and dose may have an influence on the benefits and harms associated with selective and non-selective NSAIDs, though data are limited and somewhat inconsistent. For rofecoxib, the VIGOR trial found that an increased risk of cardiovascular events appeared to become apparent only after 8 months of treatment.¹⁰⁶ Similarly, initial reports of the APPROVe trial appeared to show a duration-dependent effect, as the cardiovascular event rate curves for rofecoxib and placebo diverged only after about 18 months.¹³² However, a re-analysis that included originally censored events (occurring 14 days or more after discontinuation of study drug) suggests that the curves began to diverge after only 4 to 6 months, with no evidence of deviation from the proportional hazard over time.¹³³ The lack of an association with shorter duration of exposure in VIGOR could have been due in part to lack of power to detect differences due to small numbers of events. Supporting this hypothesis are two recent meta-analyses that found that risk of cardiovascular events with rofecoxib¹²⁴ or COX-2 inhibitors in general¹²⁹ did not vary according to duration of treatment. One of the meta-analyses also found that cardiovascular risk of rofecoxib did not vary according to dose.¹²⁴ However, the presence or absence of dose-dependent cardiovascular effects are difficult to analyze because 85% (84/98) of the events in patients allocated to rofecoxib in placebo-controlled trials occurred at a dose of 25 mg/day.¹²⁹

Observational data also suggests that increased cardiovascular risk with rofecoxib may occur at lower doses¹⁴⁵ and with shorter-term exposure.^{152, 261} Odds of acute MI were greater overall for rofecoxib relative to celecoxib in a case-control study of low-income Medicare beneficiaries

(mean age 79 years) exposed to treatment for ≤ 90 days.¹⁴⁵ The risk estimate for those taking rofecoxib > 25 mg (OR 1.70; 95% CI 1.07, 2.71) was greater than for those taking ≤ 25 mg (OR 1.21; 95% CI 1.01, 1.44), however.¹⁴⁵ Risk of CV events was similar for rofecoxib and meloxicam, regardless of duration, in a cohort study in which data was ascertained from an England National Health Services database using a Prescription Event Monitoring system.²⁶² In a case-control study of elderly patients in Quebec, the risk of acute myocardial infarction was highest following the first prescription of rofecoxib (adjusted RR 1.64, 95% CI 1.20 to 2.23 compared to non-use) and returned to baseline by the 8th prescription.²⁶¹

Some studies also suggest that duration of exposure and dose could influence the cardiovascular safety of celecoxib. Celecoxib was not associated with excess cardiovascular risk when compared with diclofenac or ibuprofen in the CLASS trials⁶⁰ or in meta-analyses^{105, 135} of mostly short-term trials of patients with arthritis. The long-term (33 months) APC polyp prevention trial was the first trial to clearly show an increased risk of cardiovascular events relative to placebo with celecoxib.¹⁰⁸ However, even though it's possible that the lack of an association in CLASS and earlier meta-analyses could be due in part to less risk with shorter duration of exposure, an alternative explanation is lack of power due to small numbers of events. Regarding dose-dependent effects, one recent meta-analysis¹²⁹ of 41 placebo-controlled trials found higher doses associated with greater cardiovascular risks relative to placebo ($p=0.03$), though most of the events at the highest dose (800 mg/day) came from two long-term polyp prevention trials.^{108, 263}

Analysis of the CLASS data also suggests that celecoxib was more effective at reducing GI events at 6 months compared with longer duration of exposure.⁶⁰ In fact, effects on pre-defined, serious GI complications were no longer present after 12 months, though interpretation of final results is problematic because of high withdrawal rates.⁹⁷ By contrast, in VIGOR, the GI benefit of rofecoxib compared to naproxen was seen early and sustained over the duration of the trial (median 9 months).¹⁹

One good-quality systematic review of eight trials found that higher doses of non-selective and partially selective NSAIDs were generally associated with greater efficacy for some measures of pain relief when directly compared to lower doses.²⁶⁴ Higher doses were also associated with greater withdrawals due to adverse events in two of four trials. In observational studies, the risk for GI bleeding with non-selective NSAIDs also appears to increase with higher doses.^{11, 191, 236} By contrast, the risk of bleeding associated with acetaminophen was not associated with dose in one meta-analysis of three case-control studies,²³⁶ though there was a modest dose response in another case-control study of elderly patients.²³⁵ At low over-the-counter doses, the risk of GI hospitalizations associated with aspirin, acetaminophen, and ibuprofen were similar to background rates in patients with rheumatoid arthritis or osteoarthritis in the ARAMIS database.²⁶⁵ A systematic review of observational studies found that use of aspirin and non-aspirin NSAIDs at over-the-counter doses is associated with an increased risk of GI bleeding, though the risk is lower than observed at prescription doses (approximately twofold greater risk at over-the-counter doses and sixfold or higher increases at heavy prescription levels.¹¹ One recent analysis of the Nurses' Health Study found that the risk of cardiovascular events was dose-related for both NSAIDs and acetaminophen.²³⁷

We found no studies evaluating the effects of alternative drug strategies such as intermittent dosing or drug holidays on risks and benefits of oral medication use. Although one difference between the APC trial (which found an increased risk of CV events with celecoxib) and the PreSAP trial (which reported no association) was twice-daily (APC) versus once-daily (PreSAP)

dosing, no study has directly compared such dosing strategies.¹⁰⁹ Furthermore, other studies of twice-daily dosing with celecoxib (such as CLASS⁶⁰ and ADAPT¹¹¹) reported no increase in CV risk.

Key Question 2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?

Demographic Subgroups Include Age, Sex, and Race

In general, the risk of cardiovascular, cardiorenal, and gastrointestinal adverse events associated with NSAIDs increase with age.¹³ In one UK population, for example, the risk of adverse gastrointestinal outcomes in patients taking selective or non-selective NSAIDs was 1.36 per 1,000 patient-years for all patients 25 years or older, but 4.03 per 1,000 patient-years in patients aged 65 or more.¹³⁸ Similarly, the risk of myocardial infarction was 1.71 per 100 person-years for all patients 25 years or older, but 4.57 per 100 person-years for those 65 or older.¹⁴⁶ We found no trial designed to assess whether the relative harms and benefits associated with different NSAIDs for osteoarthritis varies according to age. However, even if the relative benefits and harms associated with different drugs are consistent across age groups, the absolute effects would increase with age because of greater baseline CV and GI risk.

Studies that evaluated the efficacy and safety of selective and non-selective NSAIDs in average-risk elderly patients have generally reported similar findings compared with studies in populations with younger adults. An individual patient data meta-analysis of three celecoxib trials, for example, found effects of celecoxib 200 mg/day or 400 mg/day and naproxen 1,000 mg/day similar in elderly patients when evaluating WOMAC and SF-36 scores.²⁶⁶ For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on four of 10 components of the SF-36, while celecoxib 200 mg scored better on six, including general health. Celecoxib 200 mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study also confirmed that the overall incidence of GI adverse events was lower with celecoxib; the difference was about one event in 20 patients for celecoxib 200 mg and one in 10 for celecoxib 400 mg. Similarly, a meta-analysis of three rofecoxib trials reported similarly consistent efficacy for rofecoxib 12.5 mg or 25 mg daily compared to placebo among various subgroups defined by age, gender, race, location of osteoarthritis, baseline symptoms, and baseline functional status.²⁶⁷ Another meta-analysis found that trials of NSAIDs in patients over the age of 60 reported similar risks for GI complications compared to trials of patients under the age of 60.¹⁸³

Data suggesting differential effects of oral medications for osteoarthritis according to gender, ethnicity, or race are scant. In most of the published trials, a majority of subjects were women. As noted in the discussion of acetaminophen, results from the Nurses' Health Studies suggest that acetaminophen is associated with modest reductions in renal function in women,²⁴³ but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.²⁴⁶ The effects of different NSAIDs in specific ethnic minorities have only been evaluated in small studies. In a randomized crossover study of 25 black and

Hispanic patients on ACE inhibitors, peak increases in blood pressure were similar in patients on diclofenac compared with celecoxib.²⁶⁸ An observational study of 120 Native American patients seen in an Indian Health Service clinic in Phoenix who were switched to rofecoxib found that mean systolic blood pressure increased by 2.9 mm Hg overall (p=0.015) and by 4.8 mm Hg (p=0.009) in hypertensive patients.²⁶⁹ We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Co-Existing Diseases Include History of Previous Bleeding Ulcer Due to NSAIDs; Hypertension, Edema, Ischemic Heart Disease, and Heart Failure.

Rates of recurrent ulcer bleeding were similar for celecoxib 200 mg and the combinations of extended-release diclofenac 75 mg BID plus omeprazole 20 mg QD²⁷⁰ or naproxen 250 mg TID plus lansoprazole 30 mg QD²⁷¹ in two fair-quality, 24-week, parallel trials involving a total of 529 patients who presented with a bleeding ulcer (Table 28). There were also no differences between celecoxib and either combination therapy in other adverse events including GI, renal, and cardiovascular symptoms or in rates of withdrawals due to adverse events. One exception was that celecoxib 200 mg QD was associated with a higher rate of dyspepsia than naproxen 250 mg TID plus lansoprazole 30 mg QD.²⁷¹ The high rates of recurrent bleeding in both the celecoxib-treated patients and in the combination therapy groups—over 10 times as high as the rate in the CLASS trial— suggest that NSAIDs and coxibs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.

Table 28. Celecoxib in patients with bleeding ulcer history

Study Sample Size	Treatments	Recurrent ulcer bleeding at 6 months (difference; 95% CI)	Other adverse events	Withdrawals due to adverse events
Chan 2002 ²⁷⁰ n=287	Celecoxib 200 mg BID Diclofenac 75 mg BID plus omeprazole 20 mg QD	4.9% vs. 6.3% (-1.5%, CI -6.8, 3.8%; NS)	No differences	13.3% vs. 11.9%, NS*
Lai 2005 ²⁷¹ ** n=242	Celecoxib 200 mg QD Naproxen 250 mg TID plus lansoprazole 30 mg QD	3.7% vs. 6.3% (-2.6; CI -9.1, 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, p=0.02	10% vs. 7.4%, NS

*Includes withdrawals due to lack of efficacy

**Open trial

We found no randomized controlled trial evaluating the risk of bleeding with rofecoxib compared with celecoxib in high-risk patients. A Danish population-based case-control study of high-risk patients with previous gastrointestinal diseases found that rofecoxib (OR 2.1, 95% CI 1.2 to 3.5) and non-selective NSAIDs (OR 3.3, 95% CI 2.4 to 4.4), but not celecoxib (OR 1.3, 95% CI 0.7 to 2.8),²⁷² were associated with higher risks of upper gastrointestinal bleeding.

We found no randomized trials designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary according to underlying cardiovascular or renal risk. One recent analysis of three large polyp prevention trials of celecoxib or rofecoxib^{109, 132} and one observational study of rofecoxib²⁷³ found consistent risks for cardiovascular events among users at low and high baseline cardiovascular risk. However,

even if the relative risk of cardiovascular harms is consistent across risk groups, the absolute effects with any specific drug would be greater in patients at higher baseline risk. This is strikingly illustrated by a recent, good-quality population-based study of a very high risk group of 58,000 Danish patients with previous myocardial infarction that found hazard ratios for death of 2.80 (95% CI 2.41 to 3.25) for rofecoxib, 2.57 (95% CI 2.15 to 3.08) for celecoxib, 1.50 (95% CI 1.36 to 1.67) for ibuprofen, 2.40 (95% CI 2.09 to 2.80) for diclofenac, and 1.29 (95% CI 1.16 to 1.43) for other NSAIDs compared to non-use of NSAIDs.²⁷⁴ Because of high rates of death in this population (95 per 1000 person-years in those not using NSAIDs), the estimated number of patients needed to treat with an NSAID for one year to cause one additional death was very low, at 13 (95% CI 10-20) for rofecoxib, 14 (95% CI 10-24) for celecoxib, 45 (95% CI 29-102) for ibuprofen, and 24 (95% CI 16-45) for diclofenac.

Only a few trials have evaluated the effects of different medications on cardiovascular and cardiorenal events specifically in high-risk patients. Three randomized trials sponsored by the manufacturer of celecoxib found higher rates of hypertension or blood pressure increases in patients randomized to rofecoxib compared with patients randomized to celecoxib, but no differences in discontinuations due to adverse events or for episodes of heart failure.^{84, 85, 207} As noted earlier, the results of these trials must be interpreted cautiously because they evaluated possibly non-equivalent doses of rofecoxib and celecoxib, and because one of the trials⁸⁴ had important baseline differences suggesting inadequate randomization.

A meta-analysis funded by the manufacturer of rofecoxib found that in a high-risk subgroup of patients in whom aspirin was indicated (history of cardiovascular disease), rofecoxib was not associated with an increased risk of myocardial infarction compared with either placebo or non-selective NSAIDs.¹²³ However, the duration of the included trials may have been too short (median 3½ months) to detect an increased risk, few events were observed, and only a minority of patients received the high dose of rofecoxib evaluated in the VIGOR trial.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. A recent, good-quality population based retrospective cohort study, however, found that the risk of death and recurrent congestive heart failure was higher in patients prescribed NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) or rofecoxib (HR 1.27, 95% CI 1.09 to 1.49), each compared with those prescribed celecoxib.²¹¹ We also found no trials comparing the risks and benefits of different oral medications in patients with known renal failure.

Concomitant Anticoagulant or Aspirin Use

Concomitant anticoagulants. Concomitant use of anticoagulants and non-selective NSAIDs increases the risk of GI bleeding three- to six-fold compared to anticoagulants alone.^{275, 276} Several observational studies have evaluated whether COX-2 selective agents are associated with a lower risk for bleeding compared with non-selective agents in patients on anticoagulation.

A good-quality nested case-control study of elderly (>66 years old) patients on warfarin in Ontario, Canada, evaluated the association between hospitalization for upper gastrointestinal bleeding (361 cases) and use of selective or non-selective NSAIDs.²⁷⁷ It found that after adjustment for potential confounders (antiplatelet agents, hypoglycemic agents, glucocorticoids, gastroprotective agents, history of previous bleed, and comorbidities), recent use of non-selective NSAIDs (OR 1.9, 95% CI 1.4 to 3.7), celecoxib (1.7, 95% CI 1.2 to 3.6), and rofecoxib (2.4, 95% CI 1.7 to 3.6) were all associated with increased and overlapping risks for upper gastrointestinal bleeding, compared with non-use. Because this study relied on pharmaceutical

databases to identify exposures prior to hospitalization, it could not assess the confounding effects of over-the-counter use of aspirin, other NSAIDs, or acid suppressive medications. It also was unable to control for variations in INR level and the risk for bleeding.

A smaller, fair-quality nested case-control study of patients in the Netherlands evaluated the risk of bleeding in anticoagulated patients receiving partially selective (meloxicam or nabumetone) COX-2 inhibitors or non-selective NSAIDs.²⁷⁸ No case (N=154) received either celecoxib or rofecoxib. This study also differed from the Ontario study in that it included all cases of minor visible bleeding, hematoma, or black tarry stools. It used a questionnaire to assess exposure status and comorbidities. Patients were interviewed over the phone if answers were incomplete or unclear. The response rates were significantly higher in the cases (approximately 70%) compared with controls (approximately 31%). The study found that non-selective NSAIDs were associated with an increased risk of bleeding compared with partially selective NSAIDs after adjustment for duration of use and INR level (OR 3.07, 95% CI 1.18 to 8.03).

An open, crossover trial compared celecoxib 200 mg and rofecoxib 25 mg in 18 patients with OA, RA, or chronic pain who were stable (three consecutive INRs within 15% of each other) on warfarin therapy.²⁷⁹ The trial was designed to measure mean change in INR and safety parameters. Similar rates of edema, heart failure and other adverse events were found for celecoxib and rofecoxib. The INR increased by 5% to 15% between weeks one and three for both coxibs. Four minor bleeds were reported; none were associated with a significant decrease in hemoglobin concentration.

Postmarketing case reports of serious bleeding events, some fatal, have also been reported with concomitant anticoagulation and both rofecoxib and celecoxib. Most of these events occurred in elderly patients.^{135, 280}

We found no studies evaluating risks and benefits of concomitant anticoagulants and aspirin in patients with arthritis. Combination therapy has been studied in patients with indications for thromboembolic prophylaxis. However, the results of those studies are not directly applicable to patients with arthritis because of important differences in the populations (particularly with regard to cardiovascular risk), and because aspirin was used in lower, prophylactic doses (rather than anti-inflammatory and analgesic doses). One fair-quality meta-analysis (did not evaluate quality of included trials) found major bleeding risk increased with warfarin plus aspirin versus warfarin alone (at the same intensity) in patients with mechanical heart valves (3 trials, RR 1.58, 95% CI 1.02 to 2.44).²⁸¹ In patients with recent myocardial infarction or atrial fibrillation (one trial each), the increase in risk was not statistically significant (RR 3.07, 95% CI 0.33 to 28.38 and RR 2.13, 95% CI 0.20 to 23.03, respectively). In patients with mechanical heart valves, the increase in bleeding risk was offset by a reduction in thromboembolic events (RR 0.33, 95% CI 0.19 to 0.58), and there was no difference in all-cause mortality (RR 0.78, 95% CI 0.29 to 1.83). Other evidence on the risks and benefits of combination therapy has focused on comparing warfarin plus aspirin to aspirin alone. A recent good-quality meta-analysis of 10 trials, for example, found that the combination of warfarin plus aspirin increased the risk of major bleeding compared with aspirin alone following myocardial infarction or the acute coronary syndrome (RR 2.5, 95% CI 1.7 to 3.7).²⁸² However, the increase in bleeding risk was offset by lower risks for myocardial infarction, ischemic stroke, and revascularization. Mortality did not differ.

No study evaluated risk of bleeding in anticoagulated patients on acetaminophen compared with those on NSAIDs. A small, randomized controlled trial found acetaminophen associated with greater increases in INR levels compared with placebo.²⁸³ Several observational studies

have also found an association between excess anticoagulation and use of acetaminophen.^{284, 285} However, changes in INR are not the only important factor for predicting increased risk of bleeding. NSAIDs, for example, also affect platelet function and disrupt the gastric mucosal lining. Studies evaluating actual bleeding complications are necessary to better assess the comparative risks from acetaminophen and other NSAIDs.

No studies evaluated risk of bleeding in anticoagulated patients on glucosamine, chondroitin, or topical agents.

Concomitant aspirin. Beneficial effects of COX-2 selective inhibition on GI complication rates may be attenuated or eliminated by the concomitant use of aspirin. In the 20 per cent of patients in the CLASS trial who took aspirin in addition to their study drug, there was no difference in ulcer complications or ulcer complications plus symptomatic ulcers in patients randomized to celecoxib versus those randomized to diclofenac, ibuprofen, or the two NSAID comparators combined.⁹⁶ Similarly, a meta-analysis of randomized controlled trials found that beneficial effects of celecoxib on risk of endoscopically detected ulcers were reduced in patients on prophylactic aspirin (RR 0.49, 95% CI 0.28 to 0.86) compared with those not on aspirin (RR 0.27, 95% CI 0.16 to 0.48).⁶¹ This analysis excluded the results of the CLASS trials because they did not evaluate endoscopic ulcers as an outcome and because of high, differential withdrawal rates. A re-analysis that included the full CLASS trials results found no benefit (rather than a reduced benefit) from celecoxib in patients on aspirin (RR 0.96, 95% CI 0.63 to 1.46),²⁸⁶ but the appropriateness of combining data from trials reporting endoscopic ulcers with data from the CLASS trials on withdrawal rates, symptomatic ulcers, and ulcer complications, is disputed.²⁸⁷ Another meta-analysis found that use of aspirin increased the rate of endoscopic ulcers by about 6% in patients randomized to celecoxib (4.2% without aspirin and 9.9% with aspirin) and in those randomized to a non-selective NSAID (17.6% and 23.8%).⁶² In the TARGET trial, no reduction in ulcer complications with lumiracoxib compared to non-selective NSAIDs was observed in the subgroup of patients on aspirin (HR 0.79, 95% CI 0.40, 1.55).¹⁷⁵

There is less evidence on the effects of aspirin on the GI risk associated with rofecoxib. A recent trial that randomized osteoarthritis patients to placebo, enteric-coated aspirin (81 mg/day), rofecoxib 25 mg/day + aspirin 81 mg/day, or ibuprofen 2,400 mg/day found similar rates of endoscopic ulcers in the rofecoxib + aspirin arm (16.1%) and the ibuprofen alone arm (17.1%); both rates were significantly higher than the placebo (5.8%) and aspirin alone (7.3%) arms.²⁸⁸ A meta-analysis of aspirin users in two trials comparing celecoxib 200 mg daily and rofecoxib 25 mg daily found celecoxib associated with a lower rate of withdrawals due to GI adverse events than rofecoxib (0.7% vs. 3.9%, $p < 0.05$), as well as with GI symptoms.²⁸⁹ However, there were no reported serious GI events. Interpretation of these results is limited by nonequivalent dosing of the COX-2 inhibitors, pooling of data across trials, and post-hoc subgroup analyses of the aspirin-users data.

Concomitant aspirin use has not been shown to eliminate or reduce excess cardiovascular risks associated with COX-2 inhibitors. In large polyp prevention trials of rofecoxib¹³² and celecoxib,¹⁰⁹ use or non-use of low-dose aspirin did not affect the observed increased risk of thrombotic events.¹³² A recent meta-analysis of 84 placebo-controlled trials that permitted aspirin (including the polyp prevention trials) found a very similar risk of vascular events among those using aspirin (RR 1.57, 95% CI 0.90 to 2.72) and aspirin non-users (RR 1.51, 95% CI 1.14 to 2.01), though the absolute rate of events was higher in aspirin users (1.9%/year versus 1.1%/year).¹²⁹ Consistent with these findings, two large observational studies using the UK

GPDR¹⁸⁵ and QRESEARCH¹⁴⁶ databases found no significant interaction between concurrent NSAID and aspirin use and the risk of myocardial infarction. One observational study found that in patients with known cardiovascular disease, there was a higher rate of overall mortality (adjusted hazard ratio 1.93, 95% CI 1.30 to 2.87) and cardiovascular death among users of ibuprofen plus aspirin compared with users of aspirin alone, suggesting that ibuprofen (or other NSAIDs) could interfere with the cardioprotective effects of aspirin.²⁹⁰ However, this study only evaluated small numbers of patients on NSAIDs, and did not adjust for important comorbidities.

Key Question 3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Misoprostol, standard- and double-dose H2 blockers and PPIs were all effective in reducing the risk of NSAID-associated endoscopic gastric and duodenal ulcers relative to placebo in three good-quality systematic reviews (Table 29)²⁹¹⁻²⁹³ of numerous randomized controlled trials of OA/RA patients.^{9, 69, 291, 294-321} H2 blockers,³²⁰⁻³³⁰ misoprostol (RR 0.36, 95% CI 0.20 to 0.67), and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers, but not serious cardiovascular or renal illness or death.²⁹³

Misoprostol has been studied most extensively and is the only agent proven to decrease risk of ulcer complications (MUCOSA).³¹⁷ In a large, good-quality trial, misoprostol was associated with a rate of definite ulcer complications of 25/4404 (0.6%) compared to 44/4439 (0.9%) with placebo (p=0.049).³¹⁷ However, misoprostol is also the only agent to be associated with a significant risk of treatment withdrawal due to nausea (RR=1.30, 95% CI 1.08 to 1.55), diarrhea (RR=2.40, 95% CI: 2.05 to 2.81), and abdominal pain (RR=1.36, 95% CI 1.20 to 1.55).

Table 29. Placebo-controlled trials of gastroprotective agents²⁹¹⁻²⁹³

Treatment	# PCT studies Duration	Prevention of endoscopic ulcers		Prevention of clinical GI events*
		Gastric	Duodenal	
Misoprostol	1-1.5 months: 8 ≥ 3 months: 11	1-1.5 months: RR=0.17, 95% CI: 0.09 to 0.31 3 months: RR=0.26; 95% CI 0.17 to 0.39	1-1.5 months: RR=0.28; 95% CI 0.09-0.31 3 months: RR=0.47, 95% CI 0.33 to 0.69	Silverstein 1995 (MUCOSA): OR 0.598; 95% CI 0.364 to 0.982
H2 blockers	Standard doses (150 mg): 7 Double doses (300 mg): 3 1-3 months	Standard dose: insignificant effect Double dose: RR=0.44, 95% CI: 0.026 to 0.74	Standard dose at 1 and 3 months: RR=0.24, 95% CI: 0.10 to 0.57 and RR=0.36, 95% CI: 0.18 to 0.74 Double dose: 0.26, 95% CI 0.11 to 0.65	None
PPIs	4 Duration NR	RR=0.40, 95% CI 0.32 to 0.51	RR 0.19, 95% CI 0.09 to 0.37	None

*Upper GI hemorrhage, perforation, pyloric obstruction, death)

Table 30 reflects the results from five trials^{306, 309, 314, 319, 321} that directly compare one gastroprotective agent with another, as reported in the Canadian Coordinating Office for Health Technology Assessment review.²⁹² Both misoprostol and omeprazole were superior to ranitidine for the prevention of gastric ulcers. Omeprazole and lansoprazole also appeared superior to misoprostol and ranitidine for the prevention of duodenal ulcers.

Table 30. Head-to-head trials of gastroprotective agents²⁹²

Comparison	Reductions in ulcer risk	
	Gastric	Duodenal
Misoprostol vs. ranitidine* (2 trials; n=600)	RR=0.12 95% CI 0.03 to 0.89	No differences
Omeprazole 20 mg vs. ranitidine 150 mg (1 trial, n=425)	RR=0.32 95% CI 0.17 to 0.62	RR=0.11 95% CI 0.01 to 0.89
PPI** vs. misoprostol***	No differences	RR=0.29 95% CI 0.15 to 0.56

*standard dose

**omeprazole or lansoprazole

***secondary prophylaxis trials

A good-quality meta-analysis of 26 trials found co-administration of a PPI with a non-selective NSAID associated with a greater reduction in dyspepsia, epigastric pain and nausea than a selective COX-2 inhibitor alone, when each was compared to a non-selective NSAID alone (relative risk reduction 66% and absolute risk reduction 9% for the PPI + non-selective NSAID versus RRR 12% and ARR 3.7% with COX-2 inhibitor).³³¹

Key Question 4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?

Topical NSAIDs - Efficacy

Four trials directly compared topical and oral NSAIDs for osteoarthritis. Two recent good-quality systematic reviews^{332, 333} included three³³⁴⁻³³⁶ of these trials (an older systematic review was excluded because its results appear outdated.³³⁷). One systematic review (by Lin et al³³²) only included osteoarthritis trials, while the other systematic review (by Mason et al³³³) included osteoarthritis and other chronic pain conditions. The systematic reviews also used different methods for abstracting and pooling efficacy data. Specifically, the primary outcome in Mason et al was a dichotomous outcome: the proportion of patients with clinical success (defined as approximately a 50% reduction in pain) at the end of the trial. By contrast, the primary outcome used by Lin et al was continuous: the difference in standardized effect sizes for the outcomes of pain, function, or stiffness measured at the end of each week of treatment. Two^{335, 336} of the trials received 5 out of 5 points on the Jadad quality scale; the third³³⁴ received a score of 3.³³³ Mason et al found topical and oral NSAIDs equivalent for clinical success after 3 to 4 weeks

(pooled relative risk 1.1; 95% CI 0.9 to 1.3).³³³ Although Lin et al found topical NSAIDs inferior to oral NSAIDs for pain and function after one week of treatment, this finding was based on data from only one RCT (effect size -0.38 for pain, 95% CI -0.66 to -0.10 and ES -0.32 for function, 95% CI -0.60 to -0.04).³³² There were no significant differences between topical and oral NSAIDs after 2 (one RCT), 3 (two RCTs) or 4 (one RCT) weeks. Effect sizes could not be calculated for one of the three RCTs.³³⁴

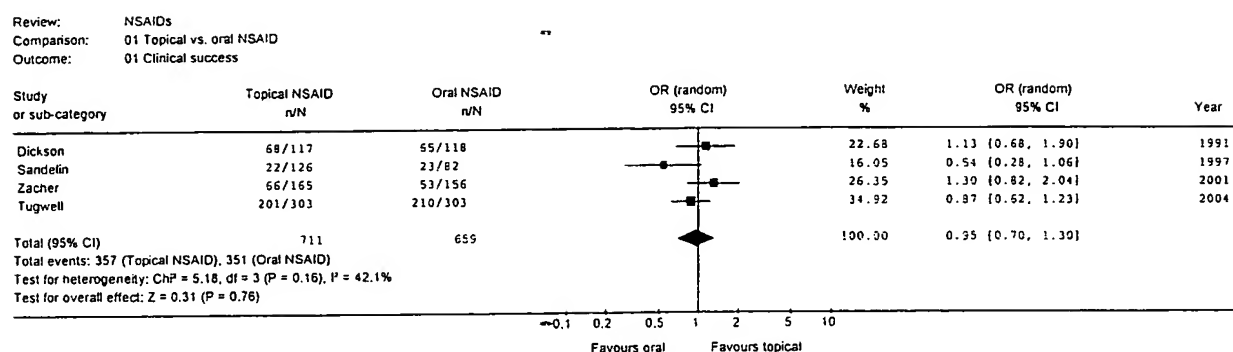
The largest and longest trial (by Tugwell et al) comparing topical and oral NSAIDs was published in 2004—too late to be included in the systematic reviews.³³⁸ This good-quality study found the proportion of responders (as defined by Outcomes Measures in Arthritis Clinical Trials and the Osteoarthritis Research Society V4 recommendations) at 12 weeks similar in patients randomized to topical or oral diclofenac (66% vs. 70%, $p=0.37$). There were also no clinically relevant differences for the outcomes of mean change in pain scores, physical function, or patient global assessment. The topical diclofenac evaluated in this trial was a proprietary formulation with DMSO (a drug not approved for topical use in humans by the FDA) not available in the U.S.

We pooled rates of clinical response from the four trials (including Tugwell et al) comparing topical and oral NSAIDs, using intention-to-treat (missing values=failure) results and methods similar to the Mason meta-analysis. We found no differences between topical and oral NSAIDs (OR=0.95, 95% CI 0.70-1.30). It should be noted that the Sandelin study, which reported the lowest efficacy for topical versus oral NSAIDs, evaluated topical eltenac, a drug that is no longer being investigated for use in humans.³³⁵

Table 31. Head-to-head trials of topical versus oral NSAID for osteoarthritis

Author, year	Condition Number enrolled	Comparison	Duration of study	Definition of clinical success
Dickson, 1991 ³³⁴	OA of knee 235	Piroxicam 0.5% Ibuprofen 400 mg po tid	4 weeks	Patient global assessment 'good' or 'excellent'
Sandelin, 1997 ³³⁵	OA of knee 208	Eltenac 1% gel Diclofenac 50 mg bid	4 weeks	Physician global assessment 'good'
Zacher, 2001 ³³⁶	OA of fingers 321	Diclofenac 1% gel Ibuprofen 400 mg po tid	3 weeks	$\geq 40\%$ improvement in pain on 100 mm VAS
Tugwell, 2004 ³³⁸	OA of knee 622	Diclofenac 1.5% in carrier with 45.5% DMSO Diclofenac 50 mg po tid	12 weeks	OMERACT VI criteria ³⁸ for clinical responder

Figure 1. Clinical success in trials comparing a topical versus an oral NSAID



Only three small (sample sizes 40, 85, and 129), short-term (2- to 4-week) trials directly compared different topical NSAIDs for chronic pain conditions. They found no differences between topical diclofenac and indomethacin,³³⁹ topical flurbiprofen and piketoprofen,³⁴⁰ or topical ketoprofen and diclofenac.³⁴¹

The two systematic reviews came to somewhat different conclusions regarding the efficacy of topical NSAIDs compared with placebo. Lin et al found that topical NSAIDs were effective only during the first 2 weeks of treatment.³³² However, their conclusions at 3 and 4 weeks were entirely based on three trials that evaluated eltenac gel (no longer produced or studied for human use) or a topical salicylate (no longer classified as a topical NSAID). Mason et al, on the other hand, found NSAIDs superior to placebo (relative risk for improvement in symptoms 1.9, 95% CI 1.7 to 2.2) from 14 placebo-controlled trials of varying duration, with a number needed to treat for one case of clinical success (approximate 50% reduction in pain) of 4.6 (95% CI 3.8 to 5.9).³³³ Results were not sensitive to quality ratings, trial sample size, outcome measured, or condition (knee osteoarthritis versus other-musculoskeletal conditions).

Four placebo-controlled trials of topical NSAIDs for osteoarthritis³⁴²⁻³⁴⁵ have been published since the systematic reviews were conducted. Three of these trials lasted longer than 4 weeks, and all found topical NSAIDs effective. The results of these trials are summarized in Table 32 for the dichotomous outcome “clinical success.” The longest trial of topical versus oral NSAIDs—a 2-year study of topical versus oral ibuprofen funded by the UK Health Technology Assessment Program—will not be completed until 2007.³⁴⁶

Table 32. Clinical success rates in recent placebo-controlled trials of topical NSAIDs

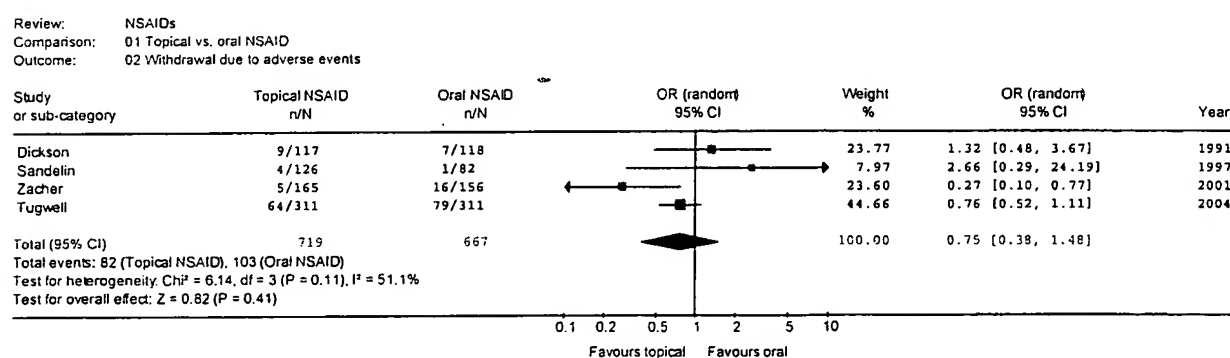
Study	Duration	Definition of 'clinical success'	Treatment group	Proportion of subjects classified as 'clinical success' at end of study period
Bookman, 2004 ³⁴³	4 weeks	>50% reduction in pain	Diclofenac Vehicle-control Placebo	44/84 (52.4%) 26/79 (32.9%) 28/84 (33.3%)
Roth, 2004 ³⁴⁴	12 weeks	>50% reduction in pain	Diclofenac Vehicle-control	79/163 (48.5%) 55/159 (34.6%)
Baer, 2005 ³⁴²	6 weeks	>50% reduction in pain	Diclofenac Vehicle-control	46/105 (43.8%) 27/107 (25.2%)
Trnavsky, 2004 ³⁴⁵	7 days	Reduction of >18 mm in VAS or >23% from baseline for pain	Ibuprofen Placebo	21/25 (84.0%) 10/25 (40.0%)

Placebo-controlled trials also suggest that topical NSAIDs differ with regard to efficacy. Topical diclofenac, which has been evaluated in the most (eight) trials, was consistently superior to placebo or associated with a trend towards superiority.^{333, 342-344} Several of these trials evaluated a proprietary compound (not available in the U.S.) of topical diclofenac in a carrier containing DMSO (Pennsaid®).³⁴⁷ Ibuprofen was superior to placebo for chronic pain conditions in three RCTs.^{333, 345} By contrast, evidence regarding the efficacy of other topical NSAIDs for chronic conditions is much more scant (see Mason,³³³ Additional Files 4 and 5). Four trials found topical piroxicam no better than placebo, homeopathic gel, or glyceryl trinitrate 1% cream. One RCT found topical ketoprofen no better than placebo. Topical felbinac, flufenamate, and indomethacin have only been evaluated in one or two small trials each. Evidence on topical flurbiprofen was mixed: one trial found topical flurbiprofen superior to placebo, but another found no differences.

Topical NSAIDs – Safety

Topical NSAIDs were associated with increased local adverse events (skin reactions such as rash, itch, and burning) compared with oral NSAIDs in two recent systematic reviews.^{332, 333} However, there were no differences for total adverse events, systemic adverse events, withdrawal due to adverse events, gastrointestinal events, or central nervous system events. For the outcome of withdrawal due to adverse events, we found no differences when we pooled the three trials included in the earlier reviews and a fourth,³³⁸ more recent trial.

Figure 2. Withdrawal due to adverse events in trials comparing a topical to an oral NSAID



Among the head-to-head trials, Tugwell et al provides the most information about adverse events because it has the largest sample size, the longest duration of follow-up, and used pre-specified definitions for adverse events and adverse-event severity.³³⁸ Topical diclofenac was associated with more local skin reactions but with fewer systemic and laboratory adverse events (Table 33).

Table 33. Adverse events from a trial comparing topical to oral diclofenac³³⁸

Adverse event	Topical diclofenac in DMSO carrier (n=311)	Oral diclofenac (n=311)	P value for difference
Withdrawal due to adverse event	21%	25%	0.15
Increase in mean blood pressure \geq 5 mm Hg	24%	28%	0.30
Dry skin	27%	1%	<0.0001
Rash	12%	2%	<0.0001
Pruritus	6%	0.6%	<0.0001
Gastrointestinal events (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, melena, nausea, vomiting)	35%	48%	0.0006
Severe gastrointestinal event (defined as producing significant impairment of functioning and definite hazard to patient's health)	2.6%	10.2%	0.0003
Melena	1%	2%	0.36
Asthma	3%	0.6%	0.02
Dizziness	0.6%	4%	0.002
Dyspnea	0%	2%	0.01
Hemoglobin went from normal to abnormal	2%	10%	<0.0001
Alanine transaminase increase to >3 times the upper limit or normal	1.1%	4.7%	0.01
Creatinine clearance went from normal to abnormal	4%	10%	0.01

No RCT was adequately designed to assess risks for serious but uncommon adverse events such as myocardial infarction, renal failure, or gastrointestinal bleeding. We identified one case-control study (1,103 cases) that evaluated the risk of hospital admission for upper gastrointestinal bleeding and perforation in patients taking topical NSAIDs.³⁴⁸ After adjusting for the confounding effects of exposure to oral NSAIDs and ulcer healing drugs, there was no association between exposure to topical NSAIDs within 45 days of an upper GI bleed (OR 1.45, 95% CI 0.84 to 2.50 with community controls and OR 1.06, 95% CI 0.60 to 1.88 with hospital controls). By contrast, oral NSAIDs were associated with increased risk (OR 2.59, 95% CI 2.12 to 3.16 for community controls and 2.00, 95% CI 1.60 to 2.50 for hospital controls). In a nested case-control study of the General Practice Research Database, topical NSAID use was not associated with symptomatic peptic ulcer (RR=1.0 versus non-use, 95% CI 0.6 to 1.7), though oral NSAID use was associated with increased risk (RR=4.0, 95% CI 3.2 to 5.1).²³⁴

We identified one case-control study of similar design that found exposure to topical NSAIDs not associated with acute renal failure (adjusted OR 1.33, 95% CI 0.79 to 2.24 using community controls and 1.04, 95% CI 0.60 to 1.83 using hospital controls).³⁴⁹ Recent exposure to oral NSAIDs, on the other hand, was associated with increased risk of renal failure using either community (adjusted OR 2.20, 95% CI 1.49 to 3.25) or hospital (adjusted OR 1.84, 95% CI 1.15 to 2.93) controls. We identified no studies comparing the risk of cardiovascular events in persons on topical versus oral NSAIDs.

Topical Salicylates (Including Capsaicin)

We identified no trials comparing topical salicylates to oral or topical NSAIDs. One recent good-quality systematic review found topical salicylates superior to placebo for pain relief when data from six trials were pooled (relative benefit 1.5, 95% CI 1.3 to 1.9; NNT 5.3, 95% CI 3.6 to

10.2).³² However, the three higher quality trials found no significant benefit (relative benefit 1.3, 95% CI 0.98 to 1.6). Local adverse events were rare, but the quality of adverse-event reporting was poor.

We identified no trials comparing topical capsaicin to oral or topical NSAIDs. One recent good-quality systematic review found that for chronic musculoskeletal pain, capsaicin was superior to placebo for achieving clinical success (defined as approximately a 50% reduction in pain), with a relative benefit of 1.5 (three trials, 95% CI 1.1 to 2.0) and number needed to treat of 8.1 (4.6 to 34).³⁵⁰ About 54% of patients had local adverse events with capsaicin, compared with 15% with placebo (relative risk 3.6, 95% CI 2.6 to 5.0). Withdrawals due to adverse events were also significantly more likely with capsaicin (13% vs. 3%, relative risk 4.0, 95% CI 2.3 to 6.8). An older systematic review was excluded because it appears outdated.³⁵¹

Chapter 4. Summary and Discussion

The table below summarizes the strength of evidence and results for each key question. Publication bias is an issue for all of these questions, because we do not know the complete details or results of unpublished trials submitted to the FDA or trials that have been conducted but not published or submitted to the FDA

Table 34. Summary of findings with strength of evidence

Key Question	Level of Evidence	Conclusion
1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?		
Efficacy: Non-selective NSAID vs. non-selective NSAID	Non-selective NSAID vs. non-selective NSAID: <i>good</i> . Consistent evidence from several good-quality systematic reviews and published trials. Salsalate vs. aspirin. <i>Poor</i> : One short-term trial. Salsalate or aspirin vs. non-aspirin NSAIDs. <i>Poor</i> .	No difference in efficacy between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac). No difference between salsalate and aspirin in one short-term trial. There were no trials or eligible observational studies of salsalate or aspirin vs. non-aspirin NSAIDs.
Efficacy: COX-2 selective vs. non-selective NSAID	Good. Consistent evidence from many published trials	No difference.
Efficacy: COX-2 selective vs. COX-2 selective	Good. Consistent evidence from six published trials.	No clinically significant differences at comparable doses.
GI and CV safety: Rofecoxib	Good. One large published trial, multiple meta-analyses and systematic reviews of published and unpublished trials, multiple observational studies.	In a pivotal, long-term trial (VIGOR) of patients with rheumatoid arthritis, rofecoxib 50 mg daily reduced symptomatic ulcers and serious ulcer complications compared with naproxen. After an average of 9 months, rofecoxib use was associated with 1 fewer symptomatic ulcer for every 62 patients treated; one fewer serious GI complication for every 191; and one additional MI for every 333 patients. The overall rate of serious adverse events, however, was higher with rofecoxib than naproxen. Higher-quality systematic reviews and observational studies are generally consistent with these findings (about 3.5 additional myocardial infarctions for every 1000 patients treated for one year). One long-term placebo-controlled polyp prevention trial also found an increased risk of MI.
GI and CV safety: Celecoxib	Fair: Multiple meta-analyses and systematic reviews of mostly short-term published and unpublished trials, multiple observational studies.	In the only published large, long-term study (CLASS), celecoxib was no better than diclofenac or ibuprofen for complicated or symptomatic ulcers at the end of follow-up. In subgroup analyses of patients not on aspirin, celecoxib was superior to ibuprofen but not to diclofenac for ulcer complications. There was no increase in the rate of cardiovascular events for celecoxib in CLASS. The overall rate of serious adverse events was similar

Key Question	Level of Evidence	Conclusion
		with celecoxib compared to ibuprofen and diclofenac. Systematic reviews and other meta-analyses of primarily short-term, unpublished data and lower doses found celecoxib superior to non-selective NSAIDs for ulcer complications. Observational studies are generally consistent with the short-term trials. However, recent meta-analyses found an increased risk of myocardial infarction with celecoxib compared with placebo (about 3.5 myocardial infarction for every 1000 patients treated for one year), with much of the evidence for increased risk coming from two large polyp prevention trials.
GI and CV safety: Valdecoxib	Fair: Fair quality meta-analyses of published and unpublished trials	Compared to non-selective NSAIDs, valdecoxib was associated with one fewer upper GI complication with valdecoxib for every 78 patients treated for 3 to 6 months. There was no association between valdecoxib and myocardial infarction in primarily short-term chronic pain trials. However, two short-term trials in a high-risk post-coronary artery surgery setting found that valdecoxib was associated with an acute two- to three-fold higher risk of cardiovascular events compared with placebo.
GI and CV safety: Etoricoxib	Fair: Several fair quality meta-analyses of published and unpublished trials	GI safety: Etoricoxib was associated with fewer perforations, symptomatic ulcers, and bleeds than diclofenac, ibuprofen, and naproxen (rate/100 patient-years 1.00 vs. 2.47). CV safety: Based on limited data from short-term trials, etoricoxib has a cardiovascular safety profile similar to non-selective NSAIDs, with the possible exception of naproxen.
GI and CV safety: Lumiracoxib	Fair: One large, long-term trial	GI safety: In patients not taking low-dose aspirin, lumiracoxib was associated with a lower risk of ulcer complications compared to naproxen and ibuprofen (1-year incidence 0.25% vs. 1.09%, $p < 0.0001$). CV safety: There were no differences in the risk of serious CV events (rates ranged from 0.11% to 0.38% after 1 year).
GI and CV safety: Partially selective NSAIDs	GI safety: Fair for meloxicam (short-term RCTs, meta-analyses, observational studies); poor for nabumetone and etodolac CV safety: Poor for all; two observational studies for meloxicam	GI safety: Meloxicam and non-selective NSAIDs were generally associated with similar risks of serious GI events; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac CV safety: Very sparse evidence that meloxicam and non-selective NSAIDs were associated with similar risks of serious CV events; no evidence for nabumetone and etodolac
GI and CV safety: Non-selective NSAIDs	Good for GI safety. Consistent evidence from many published trials, systematic reviews, and observational studies	No clear difference in GI safety between non-selective NSAIDs at commonly used doses. Naproxen was associated with a modest cardiovascular protective effect compared to other NSAIDs in a good-quality systematic

Key Question	Level of Evidence	Conclusion
	Fair for CV safety. No large, long-term controlled trials. Almost all evidence from observational studies	review of observational studies, but methodological issues could have affected the results. Comparative CV safety of other non-aspirin NSAIDs is not clear. A large systematic review of RCTs addressing this issue has not yet been published.
GI and CV safety: Aspirin	Fair. Many trials and systematic reviews, but almost exclusively in patients receiving aspirin at doses used for cardiovascular prophylaxis.	Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in prophylactic doses. There is insufficient evidence to assess safety of aspirin in doses used for pain control compared with non-aspirin NSAIDs.
GI and CV safety: Salsalate	Poor. Flawed observational data	Salsalate was associated with a lower risk of adverse events using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs. Almost no data is available on CV safety.
Mortality	Fair. Individual trials not large enough to detect differences in mortality. One meta-analysis of celecoxib using unpublished information, and one fair-quality observational study of non-selective NSAIDs.	No difference between celecoxib and non-selective NSAIDs, but few deaths occurred. In one cohort study, nabumetone was associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, edema, and impaired renal function	Fair. Multiple systematic reviews, clinical trials, and observational studies, but analyses limited by inconsistent reporting of results and probable publication bias	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. Indirect evidence and observational data suggests that rofecoxib is associated with a greater risk of hypertension, CHF, and edema compared to celecoxib. Rofecoxib was also associated with more cardiorenal events than celecoxib in three head-to-head trials of high-risk patients, but possible nonequivalent dosing limits interpretation of these results. No clear differences between celecoxib, partially selective, and non-selective NSAIDs.
Hepatotoxicity	Good. Systematic reviews of multiple trials and observational studies	Clinically significant hepatotoxicity was rare. Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. Among currently marketed NSAIDs, diclofenac was associated with a higher rate of liver-related discontinuations compared with placebo (2.17%).
Tolerability	Good for coxibs and non-selective NSAIDs (consistent results from multiple systematic reviews); fair for partially selective NSAIDs, aspirin, and salsalate (few meta-analyses and short-term trials)	Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were at least as well tolerated and aspirin was less tolerated; salsalate was less well tolerated than non-selective NSAIDs in 2 of 3 trials, but less toxic in flawed observational studies; no clear differences among coxibs or among non-selective NSAIDs
Acetaminophen	Good overall. Consistent results from multiple systematic reviews for efficacy and GI adverse events. Poor for cardiovascular safety	Acetaminophen is modestly inferior to NSAIDs for reducing pain and improving function. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies).

Key Question	Level of Evidence	Conclusion
	(no evidence on myocardial infarctions) and fair for renal safety (observational studies)	Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). Acetaminophen does not appear to be associated with an increased risk of hepatotoxicity at therapeutic doses in patients without underlying liver disease.
Glucosamine and chondroitin	Fair. Inconsistent evidence from clinical trials. The most promising results have been obtained in trials funded by a European manufacturer of pharmaceutical grade glucosamine not approved in the U.S.	A recent large, good-quality NIH-funded trial found that pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate alone or in combination were not superior to placebo among all patients studied. In a small subgroup of patients with at least moderate baseline pain, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. In older trials, many with some flaws, glucosamine was superior to oral NSAIDs and placebo in trials evaluating pharmaceutical grade glucosamine and funded by its manufacturer. Other trials found no difference between glucosamine and placebo or glucosamine and oral NSAIDs. Chondroitin was superior to placebo in older, flawed trials. Data on the effects of glucosamine on slowing progression of disease are limited to two trials showing beneficial effects on progression of knee joint narrowing. Glucosamine and chondroitin were consistently well tolerated, with no serious adverse events reported in the trials.
1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	Good for safety (consistent evidence from multiple clinical trials and observational studies), no evidence for alternative dosage strategies.	Risk of GI bleeding increases with higher doses of non-selective NSAIDs. Effects of dose and duration are somewhat inconsistent. Celecoxib was most effective for GI safety at 6 months and not after longer follow-up in the CLASS trials. A trend towards a dose-dependent CV risk of celecoxib was observed in a long-term prevention trial. CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial, but interpretation of earlier risk is imprecise because of small numbers of events. Most, but not all, observational studies suggest a dose-dependent effect of rofecoxib on MI risk.
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Good (age, sex) Poor (race)	Most studies included a majority of women. The risks of GI and CV events increase in older patients. The data that selective COX-2 inhibitors are safe and efficacious in different racial groups have been presented to the FDA. In the peer-reviewed literature, there is no evidence that the comparative efficacy of different selective and non-selective NSAIDs varies according to age, gender, or race.

Key Question	Level of Evidence	Conclusion
Pre-existing disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Previous bleeding: Good Hypertension, edema: Fair Ischemic Heart Disease: Poor (no comparative studies) Heart failure: Fair	Risk of bleeding is higher in patients with prior bleeding or PUD. Two trials found high rates of recurrent ulcer bleeding in patients randomized either to celecoxib or a non-selective NSAID + PPI. Risk of CV and renal events is higher in patients with cardiac and renal co-morbidities. In a single observational study that examined mortality, rofecoxib and non-selective NSAIDs were associated with higher rates of death and recurrent heart failure than celecoxib.
Concomitant anticoagulant use	Fair overall: Primarily observational studies	Concomitant use of anticoagulants and non-selective NSAIDs increase the risk of GI bleeding three- to six-fold. Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies, though there are case reports of serious bleeding events (primarily in the elderly). Warfarin plus aspirin (prophylactic doses) increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.
Concomitant aspirin use	Good for GI safety: Consistent evidence from clinical trials and observational studies Fair for CV safety: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on non-selective NSAIDs in one meta-analysis. In one trial, rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone (7%). Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or non-selective NSAIDs is limited, though three polyp prevention trials of rofecoxib or celecoxib found that concomitant aspirin use did not attenuate the observed increased risk of CV events.
3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Co-prescribing of misoprostol or PPIs with NSAIDs offers some advantages over full-dose H2-antagonists. PPIs are associated with the lowest rates of endoscopically detected <i>duodenal</i> ulcers. Misoprostol and PPIs are associated with similar rates of endoscopically detected <i>gastric</i> ulcers as PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of clinical GI events, it is also associated with an increased risk of GI-related adverse event withdrawals. Full-dose H2 blockers were associated with lower ulcer risk than placebo, but head-to-head trials against PPIs and misoprostol are lacking. Endoscopic duodenal ulcer risk for <i>standard</i> dose H2

Key Question	Level of Evidence	Conclusion
		blockers was lower than placebo, similar to misoprostol, and higher than omeprazole; <i>standard</i> dosages of H2 blockers and placebo were associated with similar gastric ulcer risk
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?	--	
Topical NSAIDs: efficacy	Good: Consistent evidence for selected topical NSAIDs from clinical trials	Topical NSAIDs are similar to oral NSAIDs for efficacy. Topical diclofenac is the best studied, though many trials evaluated a formulation using a DMSO carrier that is not available in the U.S. Topical ibuprofen was superior to placebo in several trials.
Topical NSAIDs: safety	Good: Consistent evidence from trials and systematic reviews and observational studies	Topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events are similar. Topical NSAIDs are superior for GI events, including severe events, and changes in hemoglobin (data from one good-quality trial).
Topical salicylates: (including capsaicin)	Fair: Only placebo-controlled trials, many of which were flawed	Topical salicylates were no better than placebo in higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

Discussion

This report provides a comprehensive summary of the comparative efficacy and safety of oral nonsteroidal anti-inflammatory drugs (NSAIDs) (selective, non-selective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease, though initial long-term trials of pharmaceutical grade glucosamine suggest an effect on radiologic evidence for disease progression.

Evidence regarding the benefits of oral NSAIDs from primarily short-term randomized controlled trials is abundant and demonstrates no clear, consistent differences for relieving pain or other osteoarthritis-related symptoms, or for superior tolerability. On the other hand, much of the uncertainty and confusion regarding NSAIDs centers on their comparative safety.

The trade-offs between reduced GI risk and increased CV harms was first clearly observed in VIGOR. In this trial, rofecoxib 50 mg daily significantly reduced symptomatic ulcers (NNT=62) and serious ulcer complications (NNT=191) compared with naproxen in patients with rheumatoid arthritis.¹⁹ However, the GI-protective effects were accompanied by a more than four-fold increase in myocardial infarctions, or one additional myocardial infarction for every 333 patients treated with rofecoxib. When considering all “serious” adverse events, moreover,

rofecoxib was not associated with any clear benefit compared with naproxen.¹¹⁴

Rofecoxib became the focus of intense scrutiny following publication of VIGOR. Subsequently, multiple observational studies^{138-141, 143-152} and systematic reviews^{124, 129} of RCTs have reported findings largely consistent with an increased risk of cardiovascular events with exposure to rofecoxib. Rofecoxib was voluntarily withdrawn from the market in 2004, after a long-term placebo-controlled polyp prevention trial reported increased cardiovascular risk.¹³² Valdecoxib was likewise voluntarily withdrawn from the market in 2005. Withdrawal was recommended by FDA based on their conclusion that valdecoxib associated with no clear GI benefit,¹¹⁷ an increased risk of serious skin reactions,¹⁶⁸ and potential increased risk of CV events.^{165, 166} As a result, celecoxib is the only selective NSAID currently available in the U.S.

The same concerns about the overall safety of rofecoxib have been directed at celecoxib. The evidence regarding the relative GI and CV safety of celecoxib, however, is less clear. In CLASS, the largest published study of GI complications, celecoxib was not significantly different than diclofenac or ibuprofen for either ulcer complications or myocardial infarctions by the end of follow-up.⁹⁴ Like the VIGOR trial, re-analysis of all serious adverse events in CLASS found no significant advantage for celecoxib.⁹⁴ On the other hand, systematic reviews and other meta-analyses of primarily short-term and frequently unpublished data found that celecoxib (primarily at lower doses than were used in CLASS) was associated with lower rates of ulcer complications than non-selective NSAIDs.^{62, 121} These findings, in combination with earlier systematic reviews of primarily short-term trials that found no increased cardiovascular risk with celecoxib, suggested a possible advantage of celecoxib over non-selective NSAIDs.^{62, 134, 135} More recent meta-analyses (including data from long-term polyp prevention trials) reporting an increased risk of myocardial infarctions with celecoxib (particularly at high doses) relative to placebo, however, raise additional questions about its appropriate use.^{129, 136}

Well-designed, long-term observational studies could provide 'real-world' information not available from most RCTs, which are usually designed as short-term efficacy trials that evaluate selected populations and employ rigid dosing regimens (often at high doses) under carefully controlled conditions. Observational studies are generally consistent with the RCTs in that celecoxib is consistently GI protective^{139, 162} or neutral¹³⁸ and not associated with higher risks of CV events relative to non-selective NSAIDs.^{144, 145, 150, 160} Additionally, celecoxib is associated with lower risks of serious GI events than rofecoxib.^{139, 142} Evidence from observational studies is less clear with regard to how celecoxib compares to rofecoxib in terms of CV risk due to differences in outcome reporting and in the number and type of factors adjusted for in outcome analyses.

An important drawback of the observational studies, however, is that they largely focus on individual adverse events in isolation. More informative analyses of the overall trade-off between risks and benefits would consider net harms from all serious adverse events. Our re-analysis of results from three studies^{139, 147, 163} reporting myocardial infarctions, heart failure hospitalizations, and gastrointestinal bleeding in an elderly Canadian population receiving multiple prescriptions suggests that in everyday use, celecoxib may confer net advantages in terms of the number of these events compared with rofecoxib and non-selective NSAIDs. However, additional studies on original data are needed to confirm this finding in other settings.

The cardiovascular effects of naproxen and other non-selective NSAIDs have been the subject of considerable debate since the publication of the VIGOR trial. At this time, among NSAIDs with sufficient evidence to assess cardiovascular risk, naproxen appears to offer the most favorable cardiovascular safety profile. In a recent, comprehensive systematic review,

naproxen (even at high doses) was moderately superior to COX-2 inhibitors for cardiovascular safety.¹²⁹ In addition, naproxen was the only NSAID (selective or non-selective) associated with a neutral cardiovascular effect relative to placebo, though these analyses were primarily based on indirect comparisons. The cardiovascular risks of non-naproxen, non-selective NSAIDs were similar to the selective COX-2 inhibitors, though most of the evidence was limited to high-dose ibuprofen and diclofenac. At this time, there is insufficient evidence to reliably judge the relative cardiovascular safety of other non-selective NSAIDs or the partially selective drugs nabumetone, diclofenac, and meloxicam. For GI safety, no clear advantage for any particular partially selective or non-selective NSAIDs has been demonstrated.

Topical NSAIDs may offer the advantages of local analgesic and anti-inflammatory effects without the systemic side effects of oral administration. They would probably be most useful in patients with a limited number of affected joints. Although topical NSAIDs appear comparable to oral NSAIDs for pain relief in several trials, the most convincing evidence comes from a recent trial that evaluated a proprietary formulation of diclofenac with DMSO that has not been FDA-approved.³³⁸ Topical NSAIDs appear safer than oral NSAIDs for GI safety, but data on comparative cardiovascular risks are not available. The relative benefits of topical rubefacients compared with topical or oral NSAIDs has not been adequately studied, and other than for capsaicin (which is sometimes classified separately from the rubefacients), there is insufficient evidence to prove that topical rubefacients are superior to placebo for osteoarthritis.

Acetaminophen is often considered an attractive alternative to NSAIDs because of its perceived safety profile. It was associated with GI-protective effects relative to non-selective NSAIDs,^{229, 231} though at the expense of modestly inferior efficacy.²³⁴ More evidence is needed to compare the effects of acetaminophen and NSAIDs on other important adverse events such as cardiovascular safety, renal dysfunction, blood pressure, and heart failure. However, one recent observational study found that heavy use of acetaminophen is associated with increased cardiovascular risks similar to that seen with NSAIDs.²³⁷ Aspirin is another alternative that has the advantage of a cardiovascular protective effect. However, nearly all of the evidence on cardiovascular and GI safety of aspirin is from trials using lower, preventative doses rather than higher anti-inflammatory and analgesic doses.

Glucosamine and chondroitin are widely available as over-the-counter supplements. The highly variable content of currently available products, however, remains a significant issue in the U.S. Further, nearly all of the trials demonstrating benefits of glucosamine have been conducted using pharmaceutical grade preparations not currently available in the U.S.²⁴⁸ Compared with the evidence for glucosamine, the evidence for chondroitin appears less promising. While these agents appear to be safe in the short term, high-quality, long-term safety data are sparse. A recent large, NIH-sponsored trial helps clarify the role of these supplements in management of osteoarthritis.²⁵⁹ It found that the combination of pharmaceutical grade glucosamine and chondroitin was modestly superior to placebo only in an analysis of a small subgroup of patients with at least moderate severity of baseline disease. Neither glucosamine nor chondroitin alone was superior to placebo overall or in the subgroup of patients with greater baseline severity. Data on effects of glucosamine on osteoarthritis progression are limited to two trials showing a beneficial effect on knee joint space narrowing over three years using a pharmaceutical grade preparation.

Strategies to reduce the risk of GI complications in patients taking NSAIDs include co-prescription of misoprostol, standard- or double-dose H2 blockers, or PPIs. All of these strategies are effective in reducing the risk of NSAID-associated *endoscopic* gastric and

duodenal ulcers relative to use of non-selective NSAIDs alone. Misoprostol (RR 0.36, 95% CI 0.20 to 0.67) and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers.²⁹³ Further, misoprostol is the only agent proven to decrease risk of clinical GI events, but is associated with an increased risk of withdrawals due to nausea, diarrhea, and/or abdominal pain.³¹⁷ In high-risk patients (those with a recent bleed), non-selective NSAIDs and the combination of a non-selective NSAID plus a PPI were both associated with similar, high rates of recurrent bleeding.^{270, 271}

In summary, each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. The role of selective and non-selective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report offers a clear overall advantage compared with the others, which is not surprising given the complex trade-offs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (cardiovascular, renal, GI, and others) involved. In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable trade-off for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and cardiovascular events), co-morbid conditions, and concomitant medication use (such as aspirin and anticoagulation). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant trade-offs.

Chapter 5. Future Research

- Nearly all of the clinical trials reviewed in this report were “efficacy” trials conducted in ideal settings and selected populations. “Pragmatic” trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- The cardiovascular safety of non-selective NSAIDs has not been adequately assessed in large, long-term clinical trials. Naproxen in particular may have a different cardiovascular safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials. The cardiovascular risks associated with the partially selective NSAIDs meloxicam, nabumetone, and diclofenac also have not been well studied.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall trade-offs between benefits and harms.
- The cardiovascular risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the cardiovascular risks have only occurred with prolonged use and at higher doses.
- Large, long-term trials of the GI and cardiovascular safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- Given the large number of patients who meet criteria for aspirin prophylaxis for cardiovascular events, more trials evaluating the effects of low-dose aspirin on GI and CV risks are needed.
- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.
- Genetic testing could theoretically help predict patients who are at higher risk of cardiovascular complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This is a promising area of future research.

- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing of certain COX-2 inhibitors could affect CV risk, this hypothesis has not yet been tested in a clinical trial.
- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the U.S. and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine. Additional long-term trials are also required to further evaluate effects of glucosamine on progression of joint space narrowing.
- No topical NSAIDs are FDA-approved in the U.S., yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO. A UK trial of topical versus oral ibuprofen is currently in progress and will help clarify the benefits and safety of topical versus oral NSAIDs. However, cohort studies using large observational databases may be required to adequately assess cardiovascular risk.

Addendum

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into our report, but their results generally appear consistent with our conclusions.

One meta-analysis evaluated risk of renal events (peripheral edema, hypertension, or renal dysfunction) and arrhythmias from 114 randomized trials of COX-2 selective NSAIDs [Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events. Meta-analysis of randomized trials. *JAMA*. 2006;296:(doi:10.1001/jama.296.13.jrv6001)]. It was rated fair-quality because it did not assess the quality of included studies. It found rofecoxib associated with increased risks of arrhythmia relative to control (placebo, other NSAID, or mixed/other) treatments (RR 2.90, 95% CI 1.07 to 7.88), though the number and rate of events was low (13/10126 or 0.1% in the rofecoxib arms, with 10 of the events ventricular fibrillation, cardiac arrest, or sudden cardiac death). The increase in risk was equivalent to about 1.1 additional arrhythmia events per 1000 patients treated with rofecoxib. Rofecoxib was also associated with an increased risk of peripheral edema (RR 1.43, 95% CI 1.23 to 1.66), hypertension (RR 1.55, 95% CI 1.29 to 1.85) and renal dysfunction (RR 2.31, 95% CI 1.05 to 5.07). For composite renal events (peripheral edema, hypertension, or renal dysfunction), risks were significantly higher with increased dose and increased duration of rofecoxib. Celecoxib was associated with lower risks of renal dysfunction (RR 0.61, 95% CI 0.40 to 0.94) and hypertension (RR 0.83, 95% CI 0.71 to 0.97) than control treatments, though there was no difference for composite renal events (RR 0.97, 95% CI 0.84 to 1.12) or arrhythmia (RR 0.84, 95% CI 0.45 to 1.57). There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and arrhythmia or renal events, though there was a trend towards increased renal events with valdecoxib/parecoxib (RR 1.24, 95% CI 1.00 to 1.55), and no arrhythmia events were reported in six trials of lumiracoxib.

Several factors complicate interpretation of estimates of arrhythmia risk from this meta-analysis. First, the rate of arrhythmias varied widely between control arms for different COX-2 selective inhibitors. For example, the rate of arrhythmias was fourteen-fold higher in the control arms of the celecoxib trials compared to the control arms of the rofecoxib trials (18/6568 or 0.3% vs. 2/10,126 or 0.01%). In addition, the proportion of specific arrhythmia events varied widely between drugs. For valdecoxib, over half (69/129 or 53%) of the arrhythmia events were atrial fibrillation, compared to 14% (3/22) for celecoxib and 8% (1/13) for rofecoxib. Finally, even though funnel plots and statistical tests did not suggest the presence of publication bias, only a minority of trials reported usable data on arrhythmia events. For example, only 10 of 37 included trials of celecoxib (accounting for about one-third of trial participants) had data that could be used in the analysis of arrhythmia events.

The second meta-analysis evaluated cardiovascular risk (primarily myocardial infarction) associated with NSAIDs from 23 observational studies (mostly of older populations) [McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296:(doi:10.1001/jama.292.13.jrv60011)]. Its results are largely consistent with our

qualitative assessment of cardiovascular risk from the observational literature. This meta-analysis appears to meet criteria for a good-quality systematic review, but its interpretation is complicated by the presence of substantial ($p \leq 0.001$), unexplained between-study heterogeneity for the main pooled analyses. It found rofecoxib associated with an increased risk of cardiovascular events at both lower (25 mg/day or less, RR 1.33, 95% CI 1.00 to 1.79) and higher (>25 mg/day, RR 2.19, 95% CI 1.64 to 2.91) doses, with the increased risk observable during the first month of treatment. Of the other NSAIDs, diclofenac (RR 1.40, 95% CI 1.16 to 1.70) was associated with the greatest cardiovascular risk, followed by indomethacin (RR 1.30, 95% CI 1.07 to 1.60) and meloxicam (RR 1.25, 95% CI 1.00 to 1.55). Celecoxib (RR 1.06, 95% CI 0.91 to 1.23), naproxen (RR 0.97, 95% CI 0.87 to 1.07), piroxicam (RR 1.06, 95% CI 0.70 to 1.59), and ibuprofen (RR 1.07, 95% CI 0.97 to 1.18) were not associated with increased risks. Only 3 of the 23 included studies reported adjusting for over-the-counter aspirin or NSAID use; two other studies included patients shortly after myocardial infarction that were all prescribed or presumed to be on aspirin.

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Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis: Data From the Third National Health and Nutrition Examination Survey

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Abstract

Objective: To estimate the prevalence of traditional risk factors for cardiovascular disease (CVD) among US adults with osteoarthritis (OA).

Methods: Using survey data from the Third National Health and Nutrition Examination Survey, we estimated the prevalence of selected CVD risk factors among a US OA and nonarthritic adult population. In additional analyses, we stratified the sample by gender and age (35-44, 45-64, and 65+ years) to further understand the CVD risk profile in an arthritic population and nonarthritic population. Relevant data on each survey participant's demographics, arthritis status, CVD risk factors, and sampling weights were obtained from the survey database.

Results: Of the 115.9 million US adults aged ≥35 years, 24.3 million (21%) have OA. Hypertension is prevalent in approximately 40% of OA patients; 20% of the patients smoke and 11% have diabetes. Prevalence of high total cholesterol is estimated to be 32%, while prevalence of low high-density lipoprotein cholesterol is estimated at 13%. Approximately 37% of OA patients are estimated to have renal impairment, but less than 1% suffer from renal failure.

Conclusion: National survey data suggest that, on average, US adults with OA have a high prevalence of cardiovascular risk factors. These findings highlight the need to consider patients' comorbidities when selecting the appropriate treatment options.

(*Am J Manag Care.* 2002;8:S383-S391)

million outpatient visits and three quarters of a million hospitalizations annually are attributable to arthritis and its treatment, with associated direct medical care costs of \$15 billion.^{1,2} Estimates of lost productivity and other indirect costs of arthritis have been estimated to be as high as \$50 billion annually.^{1,2} The clinical and economic burdens of arthritis in the United States are expected to increase as the general population ages; an estimated 60 million Americans (nearly 20% of the population) are projected to have arthritis by 2020, of whom approximately one fifth (or 12 million people) will experience meaningful activity limitation.^{1,3-5}

There is credible evidence that people with osteoarthritis (OA) and rheumatoid arthritis (RA) are at higher risk than the general population for several comorbid conditions, particularly cardiovascular disease (CVD).⁶⁻⁸ Moreover, there is an established body of research suggesting that age-adjusted mortality risk is higher among RA patients relative to the general population.⁷⁻¹⁷

The etiology of the association between arthritis and CVD is not fully understood. Various theories about the relationship have been put forth in recent studies, most of which are based on the premise that patients with arthritis are at advanced risk for development of CVD by virtue of their unfavorable risk factor profile. However, there is inherent difficulty in sorting out the relevant causes of CVD

Arthritis is a widely prevalent, disabling disease that places substantial demands on healthcare resources. It has been estimated that as many as 44

in arthritis patients as they differ from the general population in many aspects. Changes in body mass composition, changes in lipid profile associated with medication use (eg, glucocorticoids), and activity limitations resulting from chronic joint disease may all play a role in increased CVD risk.^{18,19} Some investigators believe that vascular inflammation associated with increased levels of thiol compounds and C-reactive protein, as well as peroxidization of low-density lipoprotein, may play a significant role in CVD pathogenesis in patients with arthritis.^{18,20} Medications taken for arthritis-related conditions have also been implicated for either directly or indirectly leading to atherosclerosis.^{18,21,22} The most commonly implicated drugs are glucocorticoids (chiefly, prednisone), which can increase serum lipids and glucose levels and induce hypertension.²³ Methotrexate, another commonly prescribed arthritis medication, has been shown to increase serum homocysteine levels.^{23,24}

Although national estimates of OA and RA prevalence have been reported,^{1,3,4} to the best of our knowledge the prevalence of CVD risk factors among such people has not been estimated to date. To this end, the government-sponsored database on the health status of the US population—the Third National Health and Nutrition Examination Survey (NHANES III)—was used to develop national estimates of the prevalence of selected cardiovascular risk factors among adult patients with self-reported OA and a nonarthritic US adult population.

...MATERIALS AND METHODS...

Data Source

We estimated the prevalence of selected CVD risk factors among US adults aged ≥ 35 years by diagnosis, gender, and age category (35-44, 45-64, and 65+ years) using survey data from NHANES III.²⁵

NHANES is one of the major programs in the series of health-related studies conducted by the National Center for Health Statistics, part of the US Centers for

Disease Control and Prevention, over the past 35 years. NHANES is designed to assess the health and nutritional status of adults and children in the United States through interviews and direct physical examinations. The survey is unique in that it combines a home interview with physical examinations and a variety of diagnostic and laboratory tests conducted in a mobile examination center. NHANES III, which was conducted from 1988 to 1994, included approximately 40 000 people aged ≥ 2 months selected from households in 81 counties across the 50 US states. Using a complex, stratified, multistage probability cluster sampling design (with oversampling of young children, older people, blacks, and Mexican Americans), the survey yields nationally representative information on the health and nutritional status of the civilian, non-institutionalized US population. Physical examinations and objective measures are employed when information cannot be furnished or is not available in a standardized manner through interviews or through records maintained by the health professionals who provide medical care to survey respondents.²⁵⁻²⁷

The 4 data files representing the major components of NHANES III are adult household, examination, laboratory, and dietary recall; more than 5000 data elements are collected. One section of the household adult questionnaire asks respondents to note whether a physician has told them that they have OA or RA, and when they were first told that they had the condition. Other sections of the questionnaire focus on diabetes, high blood pressure, CVD, musculoskeletal conditions, gallbladder disease, kidney conditions, respiratory and allergy conditions, vision and hearing, and dental care. Histories of smoking and chewing tobacco use are recorded on both the home adult questionnaire and examination questionnaire, while history of alcohol use is asked on the examination questionnaire. Other NHANES sections pertain to exercise, nutrition assessment, medicine/vitamin use, biochemistry values, and physical exam results. Biochemistry data collected con-

sist of hematologic tests, general biochemistry tests, urine tests, antibody tests, and diabetes testing profile. The physical exam consists of a physician's exam, dental examination, allergy skin test, audiometry, spirometry, bone densitometry, gallbladder ultrasonography, and fundus photography.^{25,26}

CVD risk factors examined in this study, as derived from the Household Adult Questionnaire (HAQ) and Laboratory Data File components of the NHANES III database, include systolic blood pressure (SBP) and diastolic blood pressure (DBP), total and high-density lipoprotein (HDL) cholesterol, physician-diagnosed diabetes mellitus, renal impairment or failure based on serum creatinine levels, and current cigarette smoking. Arthritis status was derived from the arthritis section of the HAQ as described above. Smoking status was derived from the question, "Do you smoke cigarettes now?" Diabetes mellitus status was derived from questions asking respondents whether a doctor had ever told them that they have diabetes. All other risk factor data were obtained from the NHANES III Laboratory Data File. Hypertension as a CVD risk factor was defined as SBP >140 mm Hg or DBP >90 mm Hg, as defined by current National Institutes of Health *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI) guidelines.²⁸ Renal impairment and failure were defined respectively as serum creatinine levels exceeding the upper limit and twice the upper limit of normal (ie, >1.5 mg/dL and >3 mg/dL, respectively), which reflects the methods of the Massachusetts General Hospital.²⁹

Statistical Analyses

Prevalence (stated as percentages) and associated 95% confidence intervals (CIs) were estimated for each CVD risk factor among an OA and a nonarthritic population. Gender- and age-stratified prevalence rates were also estimated for each population. SUDAAN® statistical analysis software (Research Triangle Institute,

Research Triangle Park, NC) in conjunction with Statistical Analysis System (SAS) Release 8.02 (SAS Institute, Cary, NC) were used for these analyses. SUDAAN is specifically designed for analysis of cluster-correlated data from surveys such as NHANES III that involve multistage sample designs. Robust variance estimates are generated that account for intraclass correlation, unequal weighting, stratification, and without-replacement sampling. To provide estimates that were representative of the US population, analyses of each data element incorporated sampling weights obtained from the NHANES III database. These weights account for the unequal probabilities of selection resulting from the cluster design, the planned oversampling of certain demographic subgroups, and nonresponse adjustment factors based on US Census Bureau data on age, gender, race, income, and geographic location of the US population.^{26,27} Since our investigation focused on interval estimation rather than on hypothesis testing, no tests of statistical significance were undertaken.

...RESULTS...

Prevalence Estimates

Osteoarthritis. Of the 115.9 million US adults aged ≥35 years, 24.3 million (21%) have OA (95% CI, 22.1 million-26.6 million) (Table 1). Nearly two thirds of these people are women. Prevalence rates of OA increase with age in both genders. However, the ratio of females to males with OA increases with advancing age, from 1.32:1 among people aged 35 to 44 years to 1.88:1 among people aged ≥65 years.

Table 1 also shows that the nonarthritic population is considerably younger than the OA population. Over 47% of OA patients are older than 65 years, compared with only 19% of those in the nonarthritic population. In addition, there were gender differences between the arthritis and nonarthritic populations; nearly 63% of the OA population was comprised of women, compared with only 49.9% of the general nonarthritic population.

Table 1. Estimated Numbers of US Adults Aged ≥ 35 Years With Osteoarthritis, by Gender and Age

Gender and Age (Years)	Osteoarthritis Percentage of People (95% CI)		General Population Without Arthritis Percentage of People (95% CI)	
All (n)	24 345 370	(22 110 212-26 580 528)	85 800 548	(78 999 986-92 601 110)
35-44	13.30	(11.79-14.56)	41.41	(40.18-42.47)
45-64	39.49	(39.26-39.68)	39.59	(39.74-39.46)
65+	47.21	(45.01-49.04)	18.99	(17.85-19.97)
Men (n)	9 015 680	(7 874 587-10 156 773)	42 986 882	(39 689 389-46 284 375)
35-44	15.51	(12.70-17.69)	40.13	(38.36-41.65)
45-64	40.23	(38.75-41.38)	41.17	(41.02-41.30)
65+	44.26	(42.54-45.59)	18.70	(17.63-19.62)
Women (n)	15 329 690	(13 824 691-16 834 689)	42 813 666	(38 878 456-46 748 876)
35-44	12.00	(9.99-13.66)	42.70	(41.43-43.77)
45-64	39.05	(37.58-40.26)	38.01	(37.44-38.48)
65+	48.95	(46.67-50.82)	19.29	(17.81-20.52)

CI indicates confidence interval.

Hypertension. Approximately 40% (95% CI, 35.3-45.5) of people with OA have Stage I-III hypertension as defined by the JNC VI guidelines (Table 2).²⁸ By comparison, only about 25% (95% CI, 23.0-27.6) of the general population without arthritis was estimated to have hypertension. Prevalence of hypertension is slightly higher among men than women, and, as epidemiologic data suggest, higher among people aged ≥ 65 years versus younger people.

Cigarette Smoking. Approximately 20% (95% CI, 17.6-23.1) of OA patients are current cigarette smokers (Table 2). The crude rates in this analysis are slightly lower than that for the general population without arthritis, wherein about 26% (95% CI, 23.6-28.4) are smokers.

Diabetes Mellitus. Approximately 11% (95% CI, 9.2-12.9) of people with OA have diabetes mellitus (Table 2). By comparison, only about 6% (95% CI, 5.6-7.3) of the general population without arthritis is diabetic. When stratifying by gender, this analysis suggests that female OA patients were more likely to have diabetes mellitus than a nonarthritic population. Prevalence of diabetes is slightly higher among

women than men, and, as epidemiologic data suggest, higher among older people.

Hypercholesterolemia. Approximately 32% (95% CI, 27.1-36.2) of people with OA have high total cholesterol levels (ie, ≥ 240 mg/dL) (Table 2). About 24% (95% CI, 21.4%-26.0%) of the general population without arthritis has high total cholesterol levels. Prevalence of high total cholesterol is slightly greater among women than men, and has a marked increase among people aged 45 years and older.

Low HDL Cholesterol. The prevalence of low HDL cholesterol (< 35 mg/dL) is similar, approximately 13% (95% CI, 10.8-16.1) in people with OA and 12% (95% CI, 10.4-13.2) in the general population without arthritis (Table 2). Prevalence of low HDL cholesterol is substantially higher among men than women, but there is little differentiation among the age categories.

Renal Impairment and Failure. Approximately 37% (95% CI, 31.6-41.5) of people with OA have renal impairment, manifested as serum creatinine levels exceeding the upper normal limit of 1.5 mg/dL (Table 2). Moreover, approximately 0.8% (95% CI, 0.4-1.3) of people with OA

have renal failure, defined as serum creatinine levels exceeding twice the upper normal limit (ie, ≥ 3.0 mg/dL). By comparison, it is estimated that only about 27% (95% CI, 23.8-30.3) of the general population without arthritis have renal impairment, and only 0.3% (95% CI, 0.2-0.4) have renal failure.

DISCUSSION

Patient-level examination data from the NHANES III have been used to estimate the prevalence of selected CVD risk factors among US adults with OA. Other studies assessing the prevalence of arthritis in the United States have been conducted, but the prevalence of traditional risk factors for CVD among arthritis patients has not been well quantified to date.

Estimates suggest that approximately 24.3 million US adults aged ≥ 35 years have OA, and that nearly two thirds of these people are women. These estimates are consistent with what has been reported elsewhere.³

Findings suggest that US adults with OA indeed may be at an increased risk of CVD relative to the nonarthritic population. For each of the risk factors examined, except cigarette smoking, point estimates of prevalence among OA patients exceeded those of the general population. While tests of statistical significance were not performed, it was observed that the difference in risk factor prevalence versus the general population is not statistically significant at the "conventional" $\alpha = 0.05$ level.

Our findings suggest that the prevalence of hypertension is significantly greater among OA patients versus patients without arthritis. Gabriel and colleagues⁶ found the prevalence of diabetes to be 5.0% among 441 OA patients. The estimates from this study at 11% are considerably higher. This difference could be related to a different population sampling in the 2 studies.

Reports on total cholesterol levels among patients with arthritis are scant

Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥ 35 Years With and Without Osteoarthritis

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)		Prevalence, % (95% CI)	
		Osteoarthritis (n = 24 345 370)	General Population Without Arthritis (n = 115 861 005)
Hypertension (Stage I-III, JNC VI Guidelines*)			
All	40%	(35.3-45.5)	25% (23.0-27.6)
35-44	14%	(7.5-19.7)	11% (9.3-13.1)
45-64	32%	(26.4-37.3)	28% (24.6-31.5)
65+	55%	(46.8-63.5)	50% (42.9-57.8)
Men	41%	(33.4-47.7)	28% (25.1-31.0)
35-44	20%	(6.8-33.1)	14% (11.1-17.7)
45-64	33%	(22.1-43.5)	32% (27.4-36.7)
65+	55%	(45.5-64.2)	49% (41.2-56.0)
Women	40%	(34.9-45.7)	23% (19.8-25.4)
35-44	9%	(2.8-14.8)	8% (6.1-10.3)
45-64	31%	(25.1-37.3)	24% (20.2-27.2)
65+	55%	(45.7-64.8)	52% (41.8-62.6)
Cigarette Smoking			
All	20%	(17.6-23.1)	26% (23.6-28.4)
35-44	25%	(16.1-34.5)	31% (27.2-34.8)
45-64	31%	(26.1-35.9)	26% (22.6-29.3)
65+	10%	(8.1-12.2)	15% (12.3-17.8)
Men	25%	(19.5-29.9)	30% (26.9-33.2)
35-44	34%	(13.5-54.2)	36% (30.7-42.3)
45-64	35%	(24.6-44.7)	29% (24.5-34.2)
65+	12%	(8.2-16.6)	18% (13.4-22.1)
Women	18%	(15.2-20.5)	22% (19.1-24.7)
35-44	19%	(11.1-26.4)	26% (21.4-30.4)
45-64	29%	(23.0-34.5)	22% (18.2-26.2)
65+	9%	(6.4-11.5)	12% (9.9-14.8)
Diabetes Mellitus			
All	11%	(9.2-12.9)	6% (5.6-7.3)
35-44	4%	(0.7-7.2)	4% (2.3-5.1)
45-64	11%	(7.3-13.8)	7% (5.8-8.3)
65+	13%	(11.0-15.9)	11% (9.0-12.8)
Men	10%	(7.3-12.3)	7% (5.4-7.7)
35-44	0%	(-0.2-1.1)	3% (1.0-5.3)
45-64	9%	(4.2-13.5)	8% (6.0-10.0)
65+	14%	(9.8-18.1)	11% (8.8-13.2)
Women	12%	(9.5-14.1)	6% (5.0-7.5)
35-44	7%	(1.0-12.4)	4% (2.6-6.1)
45-64	12%	(7.6-15.7)	6% (4.4-7.7)
65+	13%	(10.3-16.1)	11% (7.9-13.8)
High Total Cholesterol (≥ 240 mg/dL)			
All	32%	(27.1-36.2)	24% (21.4-26.0)
35-44	22%	(11.6-32.5)	15% (12.9-17.5)
45-64	34%	(27.8-39.3)	29% (26.0-31.9)
65+	33%	(26.3-39.3)	31% (25.9-36.7)
Men	23%	(17.7-28.5)	23% (20.2-25.6)
35-44	22%	(10.5-33.9)	19% (15.7-22.5)
45-64	26%	(18.6-33.4)	27% (23.4-31.0)
65+	21%	(13.9-27.6)	21% (17.1-25.7)
Women	37%	(30.9-42.7)	24% (21.8-27.1)
35-44	22%	(8.9-35.0)	12% (9.2-13.9)
45-64	38%	(29.9-46.5)	31% (27.2-34.5)
65+	39%	(31.4-47.3)	41% (32.8-49.2)

(continued on next page)

*Systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg (NIH Publication 98-4080, November 1997).

CVD indicates cardiovascular disease; JNC VI, Sixth Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure.

Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥ 35 Years With and Without Osteoarthritis (Continued)

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)	Osteoarthritis (n = 24 345 370)		General Population Without Arthritis (n = 115 861 005)	
Low HDL Cholesterol (<35 mg/dL)				
All	13%	(10.8-16.1)	12%	(10.4-13.2)
35-44	15%	(7.9-21.5)	11%	(9.2-13.8)
45-64	14%	(10.2-17.9)	12%	(10.0-13.5)
65+	13%	(9.9-15.2)	13%	(9.8-15.6)
Men	25%	(19.3-30.9)	18%	(15.9-20.8)
35-44	29%	(12.9-44.8)	18%	(13.7-22.3)
45-64	27%	(17.6-35.6)	19%	(15.6-21.7)
65+	22%	(15.9-29.0)	18%	(14.5-22.4)
Women	6%	(5.0-7.9)	5%	(4.0-6.6)
35-44	3%	(0.1-6.6)	5%	(3.4-7.5)
45-64	6%	(4.2-8.6)	4%	(2.9-5.3)
65+	7%	(5.1-9.2)	7%	(4.2-10.2)
Renal Impairment (Serum Creatinine Levels Above ULN, 1.5 mg/dL)				
All	37%	(31.6-41.5)	27%	(23.8-30.3)
35-44	18%	(11.1-25.0)	19%	(14.9-22.7)
45-64	28%	(22.3-33.2)	27%	(23.2-30.5)
65+	50%	(42.1-57.2)	46%	(39.1-53.5)
Men	38%	(31.3-44.1)	29%	(25.8-32.8)
35-44	24%	(9.0-38.3)	22%	(16.6-26.6)
45-64	26%	(18.0-35.0)	29%	(24.5-33.8)
65+	53%	(42.8-63.4)	47%	(39.2-54.5)
Women	36%	(30.3-41.5)	25%	(21.1-28.5)
35-44	14%	(8.0-19.1)	16%	(12.5-19.8)
45-64	28%	(21.6-35.3)	24%	(19.6-28.9)
65+	48%	(39.2-56.4)	46%	(37.0-54.4)
Renal Failure (Serum Creatinine Levels $2\times$ ULN ≥ 3.0 mg/dL)				
All	0.8%	(0.4-1.3)	0.3%	(0.2-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.0-0.1)
45-64	0.2%	(0.0-0.5)	0.1%	(0.0-0.2)
65+	1.6%	(0.6-2.6)	1.0%	(0.5-1.4)
Men	1.0%	(0.2-1.8)	0.2%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.0%	(0.0-0.1)
45-64	0.3%	(-0.1-0.7)	0.2%	(0.0-0.3)
65+	2.0%	(0.1-3.9)	0.9%	(0.2-1.5)
Women	0.8%	(0.2-1.3)	0.3%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.1-0.1)
45-64	0.2%	(-0.1-0.5)	0.1%	(0.0-0.1)
65+	1.4%	(0.3-2.6)	1.0%	(0.2-1.9)

CVD indicates cardiovascular disease; HDL, high-density lipoprotein; ULN, upper limit of normal.

and somewhat contradictory. A prevalence rate of 32% was estimated in OA patients, which is higher than the 23% rate estimated for the general population. The comparatively lower prevalence of cardio-protective HDL cholesterol found in this

study is consistent with what has been reported in other studies.^{9,30-34}

Potential limitations of this study bear mention. First, it should be noted that due to the complex sampling design of NHANES III, extreme variability in the weights has the potential to result in reduced reliability of the estimates. However, the NHANES III sample was designed to minimize the variability in the weights through measures such as weight trimming. Although unlikely, extreme observations in conjunction with large weights may have resulted in extremely influential observations dominating the analyses.²⁷ Data from the NHANES surveys are considered by health services researchers to be among the most suitable-to-task for purposes of generating national estimates of disease incidence and prevalence. Nonetheless, because NHANES III is based on surveys of the civilian noninstitutionalized population, which represents 98% of the total US population, certain groups (eg, the institutionalized elderly) were excluded.³ Although the NHANES sampling methodology accounts for factors such as this, estimates of disease and risk factor prevalence presented in this article could differ somewhat from true prevalence.

Identification of comorbid medical conditions in NHANES III is derived mainly from patient self-report rather than from physical examination. Moreover, the self-reported data are confirmed by physicians only in certain circumstances. The validity of using self-reports of arthritic conditions to estimate true prevalence of OA is unknown, but studies conducted in other disease areas suggest that self-reported measures selected from NHANES can be quite reliable. The sensitivity and specificity of self-reported hypertension in NHANES III has been assessed,³⁵ and the validity of using NHANES data in this fashion for surveillance of hypertension trends in the US population is well established. Also, self-reports of an arthritis diagnosis derived from NHANES data have been used to examine the association between arthritis incidence and use of estrogen replacement therapy, body mass index,

and weight change,^{36,37} and to explore associations between arthritis diagnosis, educational attainment, and mortality.³⁸⁻⁴⁰

Because many people with arthritis may not consult a physician for their condition, they consequently may not be able to affirmatively answer the NHANES question regarding whether a doctor has told them they have arthritis. Furthermore, the possibility of faulty recall or other ascertainment bias among NHANES III participants cannot be ruled out. Patients whose health histories span many years may omit less serious health conditions, misplace dates of occurrence, or incorrectly remember the names of health conditions that were diagnosed several months or years in the past. Certainly, poor communication or a lack of understanding of medical terminology could be detrimental factors. Patients mistaking "rheumatism" for "rheumatoid arthritis" could be one example. A related concern is that the terms used to name or describe a given health condition vary among people of different language, cultural, social, or educational backgrounds. Compounding this problem is the fact that NHANES uses a checklist to collect information on chronic conditions and does not include definitions of the terms or lists of related symptoms to provide a consistent definition across subjects. However, NHANES has a deserved reputation for its clear, unambiguous diagnostic criteria and wording on its questionnaires. Although the self-reported information regarding arthritis in NHANES III has not been systematically validated, NHANES patient data has been used to ascertain prevalence of chronic disease, including arthritis, with wide acceptance since the 1970s. Self-reported rheumatoid arthritis was excluded from this analysis because it is unlikely that patients would be able to reliably report this diagnosis for all the reasons listed above.

Finally, one of the major limitations of this study was the relatively limited number of CVD risk factors that could be estimated using the NHANES III database. Interestingly, McEntegart and colleagues⁹ and Wållberg-Jonsson and colleagues^{18,41}

in their studies of RA patients identified significant correlations between RA and several thrombotic predictors of CVD that we were not able to derive from NHANES III data, including fibrinogen, von Willebrand factor, plasminogen activator inhibitor 1, tissue plasminogen activator antigen, and fibrin D-dimer. Current thinking is that inflammatory factors that promote atherogenesis and thrombogenesis may play important roles in the development of CVD in arthritis patients, particularly those with RA. Had it been possible, estimation of prevalence rates for these potential risk factors would have been worthwhile.

...CONCLUSION...

National survey data suggests, on average, US adults with OA have a high prevalence of CVD risk factors, which is higher than that of a nonarthritic population. These differences are likely to be due to the different age and gender distributions between an arthritic and nonarthritic population. Prevalence estimates, such as the ones reported here, are not conclusive evidence that OA increases the likelihood of developing CVD risk factors or CVD. If anything, they provide further evidence that CVD and arthritis may represent separate end points of a similar pathological process.^{42,43} While the importance of CVD risk factor reduction in all people is obvious, these prevalence estimates demonstrate that from a practical clinical perspective, modifiable CVD risk factors need to be aggressively managed in the arthritic population. It is important to be aware of the higher prevalence of CVD risk factors in the arthritic population when selecting from the many treatment options available today.

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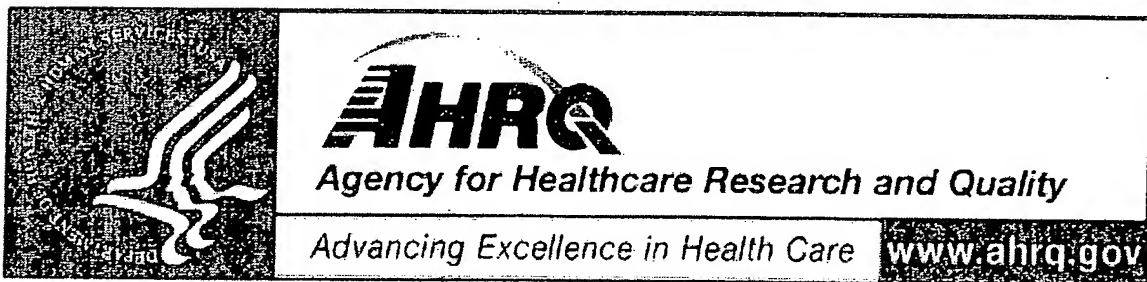
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This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Comparative Effectiveness and Safety of Analgesics for Osteoarthritis



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Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0024

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**AHRQ Publication No. 06-EHC009-EF
September 2006**

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.
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Suggested citation:

Chou R, Helfand M, Peterson K, Dana T, Roberts C. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024.) Rockville, MD: Agency for Healthcare Research and Quality. September 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Acknowledgments

We would like to acknowledge with appreciation the members of the Technical Expert Panel for their advice and consultation. In addition, we would also like to acknowledge Eric Johnson, Ph.D., for reviewing this manuscript.

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Executive Summary

Background

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life. About 6 percent of U.S. adults aged 30 years or older have symptomatic osteoarthritis of the knee, and 3 percent have symptomatic osteoarthritis of the hip. Osteoarthritis increases with age: the incidence and prevalence increase two- to tenfold from age 30 to 65 and continue to increase after age 65. The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product, with more than half of these costs related to work loss.

Common oral medications for osteoarthritis include nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. Patients with osteoarthritis also use over-the-counter supplements not regulated by the U.S. Food and Drug Administration (FDA) as pharmaceuticals, including glucosamine and chondroitin, as well as topical agents. Opioid medications are also used for selected patients with refractory, chronic pain but are not recommended for first-line treatment of osteoarthritis and therefore not included in this review. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may vary for individual drugs within a class. Nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise) also help improve pain and functional status in patients with osteoarthritis.

A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the fewest serious adverse effects. NSAIDs decrease pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-1 protects the lining of the stomach from acid. COX-2 is found in joint and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis, low back pain, minor injuries, and soft tissue rheumatism. However, NSAIDs that also block the COX-1 enzyme (also called “nonselective NSAIDs”) can cause gastrointestinal bleeding. In the United States, there are an estimated 16,500 annual deaths due to NSAID-induced gastrointestinal complications, a higher death rate than that for cervical cancer or malignant melanoma. Theoretically, NSAIDs that block only the COX-2 enzyme (also called “coxibs,” “COX-2 selective NSAIDs,” or “selective NSAIDs”) should be safer with regard to gastrointestinal bleeding, but they also appear to be associated with increased rates of serious cardiovascular and other adverse effects. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain.

For this report, we defined the terms “selective NSAIDs” or “COX-2 selective NSAIDs” as drugs in the “coxib” class (celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib). We defined “partially selective NSAIDs” as other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam). Aspirin differs from other NSAIDs because it irreversibly inhibits platelet aggregation, and the salicylic acid derivatives (aspirin and salsalate)

were considered a separate subgroup. We defined “nonaspirin, nonselective NSAIDs” or simply “nonselective NSAIDs” as “all other NSAIDs.”

This report summarizes the available evidence comparing the benefits and harms of analgesics in the treatment of osteoarthritis.

Oral agents include:

- | | |
|-----------------------------------|---------------------------------|
| • Aspirin | • Ketorolac |
| • Acetaminophen | • Lumiracoxib ¹ |
| • Celecoxib | • Meclofenamate sodium |
| • Choline magnesium trisalicylate | • Mefenamic acid |
| • Chondroitin | • Meloxicam |
| • Diclofenac | • Nabumetone |
| • Diflunisal | • Naproxen |
| • Etodolac | • Oxaprozin |
| • Etoricoxib ¹ | • Piroxicam |
| • Fenoprofen | • Rofecoxib ¹ |
| • Flurbiprofen | • Salsalate |
| • Glucosamine | • Sulindac |
| • Ibuprofen | • Tenoxicam ¹ |
| • Indomethacin | • Tiaprofenic acid ¹ |
| • Ketoprofen | • Tolmetin |
| • Ketoprofen ER | • Valdecoxib ¹ |

¹ These drugs are currently not approved by the FDA for use in the United States (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) or have been withdrawn from the market (rofecoxib and valdecoxib).

Questions addressed in this report are:

1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: The only benefits considered under this question are improvements in osteoarthritis symptoms from long-term use. Evidence of harms associated with NSAID use include long-term studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.*
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?
 - Demographic subgroups include age, sex, and race.
 - Coexisting diseases include hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous bleeding due to NSAIDs.

- Concomitant medication use includes anticoagulants.
3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?
 4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen, and salicylate.

A summary of the findings is shown in Table A.

Conclusions

Oral NSAIDs

Benefits: improvements in osteoarthritis symptoms

- **Nonselective NSAID vs. another nonselective NSAID**
 - Many trials found no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac) in efficacy for pain relief or improvement in function.
 - In one short-term trial, salsalate and aspirin did not differ significantly in efficacy for pain relief or symptom improvement.
 - No studies evaluated the comparative efficacy of salsalate or aspirin vs. a nonaspirin NSAID.
- **COX-2 selective (NSAID) vs. nonselective NSAID**
 - COX-2 selective NSAIDs and nonselective NSAIDs did not clearly differ in efficacy for pain relief, based on many good-quality, published trials.
- **COX-2 selective NSAID vs. different COX-2 selective NSAID**
 - Celecoxib and rofecoxib did not differ significantly in efficacy for pain relief at commonly used and comparable doses, based on consistent evidence from six good-quality trials.
 - No studies compared efficacy of COX-2s other than celecoxib and rofecoxib.

Harms: gastrointestinal (GI) and cardiovascular (CV)

- **Rofecoxib vs. nonselective NSAID**

- In the only large, long-term trial (VIGOR), rofecoxib 50 mg daily caused fewer serious ulcer complications than naproxen 1,000 mg daily in patients with rheumatoid arthritis but also significantly increased the risk of myocardial infarction. The overall rate of serious adverse events was higher with rofecoxib than with naproxen.
 - There were about 16 fewer symptomatic ulcers, including 5.2 fewer serious GI complications, for every 1,000 patients treated with rofecoxib vs. naproxen after a median of 9 months of treatment.
 - There were 3.0 additional myocardial infarctions for every 1,000 patients treated with rofecoxib compared to naproxen in VIGOR.
- Rofecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of randomized controlled trials (RCTs).
 - About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with rofecoxib compared to placebo in the systematic review.
- Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks.
- **Celecoxib vs. nonselective NSAID or placebo**
 - It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months. In the only large, published trial (CLASS), celecoxib at 800 mg daily did not decrease predefined serious ulcer complications overall compared with diclofenac and ibuprofen; the risk of serious GI events was lower than with ibuprofen, but not diclofenac, at 6 months in patients who did not use aspirin; and there was no reduction in serious GI events at the end of followup. The overall rate of serious adverse events with celecoxib was similar to the rate with ibuprofen and diclofenac.
 - In fair-quality meta-analyses of arthritis trials, most of which evaluated short-term use, celecoxib caused fewer ulcer complications than nonselective NSAIDs and did not increase the risk of myocardial infarction.
 - Celecoxib 400 mg twice daily was associated with an increased risk of serious CV events (CV death or myocardial infarction) relative to placebo in a long-term trial of polyp prevention.
 - Celecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of RCTs. Most of the

CV events with celecoxib were reported in two large polyp-prevention trials evaluating 200 mg or 400 mg twice daily, or 800 mg once daily.

- About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with celecoxib compared to placebo.

- **Valdecoxib vs. nonselective NSAID or placebo**

- Valdecoxib was associated with a lower risk of upper GI complications compared with diclofenac, ibuprofen, or naproxen in two fair-quality meta-analyses of published and unpublished trials.
- There have been too few events reported in RCTs of patients with chronic conditions to accurately assess CV risk associated with valdecoxib.
- Two short-term trials in a high-risk post-coronary-artery-surgery setting found that valdecoxib was associated with a two- to threefold higher risk of CV events compared with placebo.
- Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk.

- **Etoricoxib vs. nonselective NSAID**

- Etoricoxib was associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs in a fair-quality meta-analysis of 10 trials.
- In primarily short-term trials, systematic reviews of RCTs suggest that etoricoxib has a similar CV safety profile compared to other NSAIDs, with the possible exception of naproxen. Definitive conclusions are not possible because of small numbers of CV events.

- **Lumiracoxib vs. nonselective NSAID**

- Results from one large trial (TARGET) found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen.
- There was no statistically significant difference in rates of serious CV events between lumiracoxib relative to naproxen or ibuprofen in TARGET.
- Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib.

- **Partially selective NSAID vs. nonselective NSAID**

- Meloxicam: There were no significant differences in risks of serious GI events in several meta-analyses of up to 28 primarily short-term clinical trials, and no difference in CV risk in three observational studies.
- Nabumetone or etodolac: There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety.
- **Nonselective NSAID vs. nonselective NSAID or any COX-2 selective NSAID**
 - No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.
 - The CV safety of naproxen was moderately superior to that of any COX-2 selective NSAID in a large systematic review of RCTs.
 - There were 3.3 additional myocardial infarctions for every 1,000 patients treated with any COX-2 inhibitor instead of naproxen for 1 year.
 - The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs in a large systematic review.
 - In indirect analyses, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo.
- **Aspirin**
 - Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds compared to placebo or nonuse when given in long-term prophylactic doses.
 - There is insufficient evidence to assess the balance of GI and CV safety of higher dose aspirin as used for pain relief compared with nonaspirin NSAIDs.
- **Salsalate**
 - Salsalate was associated with a lower risk of adverse events than other selective and nonselective NSAIDs using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs.
 - Almost no data are available on CV safety.

Harms: mortality

- Individual trials were not large enough to detect differences in mortality between the

included drugs.

- One meta-analysis of celecoxib found no difference between celecoxib and nonselective NSAIDs, but there were few events.
- In one fair-quality cohort study, nabumetone was associated with a lower risk of all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.

Harms: hypertension, congestive heart failure (CHF), edema, and impaired renal function

- All NSAIDs and COX-2 inhibitors can cause or aggravate these conditions.
- There is good evidence from short-term trials that, on average, nonselective NSAIDs raise mean blood pressure by about 5.0 mm Hg (95-percent confidence interval [CI] 1.2 to 8.7). However, similar average blood pressure changes may not necessarily correspond with similar likelihoods of an event requiring withdrawal, medication change, or other clinical consequences.
- Evidence from good-quality observational studies suggests that rofecoxib is associated with greater risks of hypertension, CHF, and edema than celecoxib. Indirect evidence from various meta-analyses of either rofecoxib or celecoxib vs. nonselective NSAIDs are consistent with these findings. Direct randomized trial evidence, however, is limited in quantity and difficult to interpret because of possible non-equivalent dosing of drugs. Evidence regarding the comparative risk of renal dysfunction for celecoxib and rofecoxib is sparse.
- There was weak evidence that aspirin and sulindac have less hypertensive effect than other nonselective NSAIDs.
- There were no clear differences among other selective or nonselective NSAIDs for these adverse events.

Harms: hepatotoxicity

- Clinically significant hepatotoxicity was rare.
- Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo (1 additional case for every 53 patients treated with diclofenac).

Tolerability

- Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs were better or similarly tolerated and aspirin was less well tolerated.
- There were no clear differences in tolerability among COX-2 selective or

nonselective NSAIDs.

- Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs. Available evidence is somewhat sparse and mixed, with two of three short-term trials suggesting salsalate is less well tolerated than nonselective NSAIDs and older, flawed observational studies suggesting that salsalate is less toxic than nonselective NSAIDs.

Other oral agents: benefits and harms

- **Acetaminophen**

- Acetaminophen was modestly inferior to NSAIDs for pain and function in four systematic reviews.
 - Pain severity ratings averaged less than 10 points higher for acetaminophen compared to NSAIDs on 100-point visual analog scales.
- Compared with NSAIDs, acetaminophen had fewer GI side effects (clinical trials data) and serious GI complications (observational studies).
- Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies).
- One good-quality, prospective observational study found an increased risk of CV events with heavy use of acetaminophen that was similar to the risk associated with heavy use of NSAIDs.
- Acetaminophen at therapeutic doses does not appear to be associated with an increased risk of hepatotoxicity compared to nonuse in patients without underlying liver disease.

- **Glucosamine and chondroitin**

- In one large, good-quality trial the combination of pharmaceutical-grade glucosamine hydrochloride plus chondroitin (not currently available in the United States) was not superior to placebo among all patients studied. Neither glucosamine nor chondroitin alone was superior to placebo. In an analysis of a small subgroup of patients with at least moderate baseline pain, there was a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis.
- Systematic reviews of older trials found glucosamine modestly superior to oral NSAIDs and placebo in most trials, but there was some inconsistency between trials, most trials had some flaws, and results may not be directly applicable to the United States because the positive trials primarily evaluated pharmaceutical-grade glucosamine available in Europe.

- Only 2 of 20 placebo-controlled trials assessed effects of glucosamine on radiologic disease progression. One fair- and one good-quality trial found pharmaceutical-grade glucosamine superior to placebo for progression of knee joint space narrowing over 3 years.
- Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.

Effect of dosage and duration of treatment on the benefits and harms of oral medication use

- We found no studies evaluating the GI or CV safety of alternative dosing strategies (such as alternate day dosing, once daily versus twice daily dosing, or periodic drug holidays).
- The risk of GI bleeding increases with higher doses of nonselective NSAIDs.
- The most comprehensive systematic review of RCTs found no clear association between duration of exposure and CV risk of COX-2 inhibitors. However, estimates of CV risk with shorter duration of exposure are imprecise due to low numbers of events.
- The most comprehensive systematic review of RCTs found higher doses of celecoxib associated with increased CV risk, but could not determine the effects of dose on CV risk associated with rofecoxib due to low numbers of events at lower doses. Most trials of nonselective NSAIDs involved high doses.

Differences in demographic and clinical subgroups

- GI and CV complication rates are higher among older patients and those with predisposing comorbid conditions, but there is no evidence that the relative safety of different NSAIDs varies according to baseline risk.
 - Compared to nonuse of NSAIDs, one additional death per 1 year of use occurred for every 13 patients treated with rofecoxib, 14 with celecoxib, 45 with ibuprofen, and 24 with diclofenac in one large, population-based observational study of high-risk patients with acute myocardial infarction.
- There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse.
- Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of recurrent ulcer bleeding are high (around 5 percent after 6 months) in patients prescribed celecoxib or a nonselective NSAID plus a PPI.

Concomitant anticoagulant use

- Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to sixfold compared to anticoagulants alone.
- Reliable conclusions about the safety of selective NSAIDs used with anticoagulants are not possible due to flaws in existing observational studies, although there are case reports of serious bleeding events, primarily in the elderly.

Concomitant aspirin use

- In the CLASS studies, there was no difference in rates of ulcer complications between celecoxib and nonselective NSAIDs in the subgroup of patients who took aspirin.
- Concomitant low-dose aspirin use increased the rate of endoscopic ulcers by about 6 percent in both patients on celecoxib and those on nonselective NSAIDs in one meta-analysis.
- Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers (16-17 percent), which were significantly higher than those for placebo (6 percent) or aspirin alone (7 percent).
- The most comprehensive systematic review of RCTs found that compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs.

Effects of coprescribing H2-antagonists, misoprostol, or PPIs

- Consistent evidence from good-quality systematic reviews and numerous clinical trials found coprescribing of PPIs to be associated with the lowest rates of endoscopically detected duodenal ulcers relative to gastroprotective agents.
- Coprescribing of misoprostol is associated with similar rates of endoscopically detected gastric ulcers as coprescribing of PPIs.
- While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.
- The risk of endoscopic duodenal ulcers for *standard*-dose H2 blockers was lower than placebo, similar to misoprostol, and higher than omeprazole. Standard dosages of H2 blockers were associated with no reduction of risk for gastric ulcers relative to placebo.
- *Double (full)* dose H2 blockers were associated with a lower risk of endoscopic gastric and duodenal ulcers relative to placebo. It is unknown how full-dose H2 blockers compare to other antiulcer medications because head-to-head trials are lacking.

Comparison of oral medications with topical preparations

- **Topical NSAIDs: efficacy**
 - Studies of topical NSAIDs typically evaluated proprietary formulations not approved by the FDA.
 - Topical NSAIDs were similar to oral NSAIDs for pain relief in trials primarily of patients with osteoarthritis of the knee, with topical diclofenac (often with dimethyl sulphoxide [DMSO], a drug not approved for use in humans in the United States) best studied.
 - Topical ibuprofen was superior to placebo in several trials.
- **Topical NSAIDs: safety**
 - Consistent evidence from good-quality trials, systematic reviews, and observational studies found topical NSAIDs to be associated with increased local adverse events compared with oral NSAIDs.
 - Total adverse events and withdrawal due to adverse events were similar.
 - Data from one good-quality trial found topical NSAIDs superior to oral NSAIDs for GI events, including severe events, and changes in hemoglobin.
- **Topical salicylates and capsaicin**
 - Topical salicylates were no better than placebo in higher quality placebo-controlled trials.
 - Compared to placebo, one additional patient achieved pain relief for every eight that used topical capsaicin in a good-quality meta-analysis, but capsaicin was associated with increased local adverse events and withdrawals due to adverse events.

Balance of evidence and harms

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. Each was also associated with gaps in the evidence necessary to determine the true balance of benefits vs. harms. The role of selective and nonselective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence vary, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others. This is not surprising, given the complex tradeoffs between the many benefits (pain relief, improved function,

improved tolerability, and others) and harms (CV, renal, GI, and others) involved.

Individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of an increase in CV risk, for example, could be an acceptable tradeoff for some patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation medications). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

Remaining Issues

- The CV safety of nonselective NSAIDs has not been well studied in large, long-term clinical trials. Naproxen, in particular, may be associated with fewer CV risks than other NSAIDs and should be investigated in long-term, appropriately powered trials.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall tradeoffs between benefits and harms.
- The CV risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to continue to assess the effects of dose and duration as more data become available; current estimates of risks at lower doses and with shorter duration of exposure are less precise than estimates at higher doses and longer duration of exposure because of small numbers of events.
- Large, long-term trials of the GI and CV safety associated with full-dose aspirin, salsalate, or acetaminophen compared with nonaspirin NSAIDs or placebo are lacking. Recent observational data suggesting an increased CV risk with heavy use of acetaminophen highlight the need for long-term, appropriately powered clinical trials.
- Given the large number of patients who meet criteria for aspirin prophylaxis for CV events, more trials evaluating the dose-related effects of aspirin 50-1500 mg on GI benefits and CV safety are needed.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing

of certain COX-2 inhibitors could reduce CV risk, this hypothesis has not yet been tested in a clinical trial.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical-grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations of glucosamine and chondroitin with oral NSAIDs are needed, as these are likely to remain available even if the FDA approves pharmaceutical-grade formulations.
- No topical NSAIDs are FDA approved in the United States, yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO, which is not approved in the United States for use in humans. Cohort studies using large observational databases may be required to adequately assess CV risk.

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into this report, but found their results generally consistent with our conclusions:

- A fair-quality meta-analysis of arrhythmia and renal event (peripheral edema, hypertension, or renal dysfunction) risk from 114 randomized trials of COX-2 selective NSAIDs found rofecoxib associated with increased risks of arrhythmia (primarily ventricular fibrillation, cardiac arrest, or sudden cardiac death) and renal dysfunction (peripheral edema, hypertension, or renal dysfunction) relative to control treatments (placebo, other NSAIDs, or mixed/other). The increased risk was equivalent to approximately 1.1 additional arrhythmia events per 1,000 patients treated with rofecoxib. Celecoxib was associated with lower risks of renal dysfunction and hypertension than control treatments, although there was no difference for the pre-specified, primary composite renal outcome of peripheral edema, hypertension, renal dysfunction or arrhythmia. There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and either arrhythmia or renal events (no arrhythmia events reported with lumiracoxib).
- A good-quality meta-analysis of cardiovascular risk (primarily myocardial infarction) from 23 observational studies was largely consistent with our qualitative assessment of the observational literature. It found rofecoxib associated with a dose-dependent, increased risk of cardiovascular events that was detectable during the first month of treatment. Of the other NSAIDs, diclofenac was associated with the highest risk, followed by indomethacin and meloxicam. Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. Assessments of increased risk were modest (relative risks all <2.0), and all of the main analyses were associated with substantial between-study heterogeneity.

Table A. Summary of Findings on Comparative Effectiveness and Safety of Analgesics for Osteoarthritis, with Strength of Evidence

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
COX-2 selective NSAIDs	<ul style="list-style-type: none"> Good evidence COX-2-selective NSAIDs are comparable in efficacy (pain relief) to nonselective NSAIDs. Good evidence COX-2 selective NSAIDs are comparable in efficacy to each other. 	<p>GI: Fair to good evidence of fewer serious GI events with COX-2 selective NSAIDs compared to nonselective NSAIDs, at least in the first 6 months of treatment.</p> <p>CV: Comparative data on CV risks of COX-2 selective vs. nonselective and partially selective NSAIDs are sparse, with a few exceptions (see below). Fair evidence that COX-2 selective NSAIDs are associated with increased risks of serious CV events (primarily myocardial infarction) compared to placebo. CV risks may increase with greater dosages and durations of treatment, but estimates of risks at lower doses and with shorter durations of treatment are imprecise due to small numbers of events.</p> <ul style="list-style-type: none"> Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks. Cautions about CV risk apply primarily to rofecoxib and celecoxib, as CV safety data are less precise (due to small numbers of events) for valdecoxib, etoricoxib, and lumiracoxib. <p>Other</p> <ul style="list-style-type: none"> Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk. Fair evidence suggests that rofecoxib is associated with greater risk of hypertension, CHF, edema, and cardiorenal events than celecoxib. 	<ul style="list-style-type: none"> Good evidence that risk of GI bleeding and CV events increases with age. Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities.
NSAIDs : nonselective (including naproxen), partially selective	<ul style="list-style-type: none"> Good evidence nonselective and partially selective NSAIDs are comparable in efficacy to each other. 	<ul style="list-style-type: none"> GI : Good evidence that all nonselective NSAIDs are associated with comparable, dose-dependent increases in risk of serious GI events compared to none. Good evidence that coprescription of misoprostol or PPIs can attenuate this risk, but misoprostol is less well tolerated. No clear evidence (fair for meloxicam and poor for etodolac and nabumetone) that partially selective NSAIDs are associated with decreased risk relative to nonselective NSAIDs. CV : Data on CV risks of nonselective and partially selective NSAIDs are sparse, with a few exceptions: <ul style="list-style-type: none"> Fair evidence that high doses of ibuprofen and diclofenac carry similar risks of serious CV events compared to COX-2 selective NSAIDs. Fair evidence that naproxen is associated with a lower risk of CV events than COX-2 selective NSAIDs and no excess risk compared to placebo. Other: Fair evidence that diclofenac is associated with higher rates of aminotransferase elevations than other NSAIDs. 	<ul style="list-style-type: none"> Good evidence that risk of GI bleeding and CV events increases with age. Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities. Fair evidence that using NSAIDs concomitantly with anticoagulants increases GI bleeding risk three- to sixfold.

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Aspirin/ salsalate	<ul style="list-style-type: none"> No evidence comparing efficacy of aspirin or salsalate to COX-2s or NSAIDs. 	<ul style="list-style-type: none"> Good evidence that aspirin 50-1500 mg (for thrombotic event prophylaxis) is associated with greater risks of serious GI events compared to placebo or when added to warfarin. Good evidence that low-dose aspirin is effective for preventing CV events. Insufficient evidence to assess GI and CV risks associated with higher doses of aspirin for pain control or with salsalate. 	<ul style="list-style-type: none"> Good evidence that concomitant use of aspirin attenuates or eliminates the GI benefits of COX-2 selective NSAIDs. Fair evidence that concomitant use of low-dose aspirin does not eliminate CV risks when added to NSAIDs.
Acetaminophen	<ul style="list-style-type: none"> Good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs. 	<ul style="list-style-type: none"> Good evidence of lower risk of GI complications with acetaminophen compared to NSAIDs. Fair evidence of increased risk of blood pressure and renal dysfunction with acetaminophen compared to nonuse. Poor evidence (a single observational study) that heavy use of acetaminophen carries a similar CV risk compared to heavy use of NSAIDs. 	None
Glucosamine (pharmaceutical grade)/ chondroitin	<ul style="list-style-type: none"> Fair evidence (some inconsistency between clinical trials) that pharmaceutical-grade glucosamine and chondroitin are not more effective than placebo in unselected patients, including one recent, large, good-quality trial finding no beneficial effects from glucosamine or chondroitin alone or in combination. In an analysis of a small subgroup of patients with at least moderate baseline pain in the latter trial, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. Fair evidence of no clear difference in efficacy between pharmaceutical-grade glucosamine or chondroitin and NSAIDs. No studies compared glucosamine or chondroitin to acetaminophen. 	<ul style="list-style-type: none"> Good evidence that glucosamine and chondroitin are well tolerated and do not appear to be associated with serious adverse events. 	None

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Topical NSAIDs	<ul style="list-style-type: none"> Good evidence they are comparable to oral NSAIDs for pain relief in trials primarily of patients with knee osteoarthritis. <ul style="list-style-type: none"> Most trials of topical NSAIDs evaluate proprietary formulations not available in the United States. 	<ul style="list-style-type: none"> Good evidence that topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Good evidence that topical and oral NSAIDs are comparable in rates of total adverse events and withdrawals due to adverse events. Good evidence that topical NSAIDs are associated with fewer GI events, including severe events, and changes in hemoglobin compared to oral NSAIDs. 	None
Topical salicylates and capsaicin	<ul style="list-style-type: none"> Fair evidence that capsaicin, but not topical salicylates are superior for pain relief compared to placebo. 	<ul style="list-style-type: none"> Good evidence that topical capsaicin is associated with increased local adverse events and withdrawals due to adverse events compared to placebo. 	None

Abbreviations: CHF = congestive heart failure; COX = cyclo-oxygenase; CV = cardiovascular; GI = gastrointestinal; NSAID=nonsteroidal antiinflammatory drug; PPI=proton pump inhibitor.

Chapter 1. Introduction

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.² Among U.S. adults aged 30 or older, approximately 6% have symptomatic osteoarthritis of the knee, and 3% have symptomatic osteoarthritis of the hip.³ Osteoarthritis increases with age, with the incidence and prevalence increasing 2- to 10-fold from age 30 to 65, and continues to increase after age 65.⁴ Osteoarthritis accounts for more disability in walking, stair climbing, and other tasks requiring use of the lower extremities than any other disease, particularly in the elderly.⁵ The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product,³ with more than half of these costs related to work loss.⁵

In addition to non-pharmacologic interventions (such as physical therapy, weight reduction, and exercise), numerous medications and over-the-counter supplements are available to treat pain and potentially improve functional status in patients with osteoarthritis. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs within a class. Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Appendix A). Many are available at lower over-the-counter and higher prescription doses. Commonly used supplements sold over-the-counter and not regulated as pharmaceuticals by the FDA include glucosamine and chondroitin. Topical agents frequently used by patients with osteoarthritis are rubefacients (including capsaicin), NSAIDs, and other miscellaneous preparations.⁶ Opioid medications are also used for patients with chronic pain, especially if it is refractory to other therapies, but are not recommended for first-line treatment for osteoarthritis or other conditions because of risks of addiction, tolerance, diversion, and other adverse events.^{7,8}

NSAIDs exert analgesic, anti-inflammatory, and anti-pyretic effects by blocking *cyclooxygenases (COX)*, enzymes that are needed to produce *prostaglandins*. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-2, found in joint and muscle, contributes to pain and inflammation. Because they block COX-2, non-steroidal anti-inflammatory drugs reduce pain compared to placebo in patients with arthritis,⁹ low back pain,¹⁰ minor injuries, and soft tissue rheumatism. Less is known about COX-3, which has been found in the cerebral cortex and cardiac tissue and appears to have effects on centrally-mediated pain.¹

NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the 1990s in the United States, nonaspirin NSAIDs are estimated cause 32,000 hospitalizations and 3,200 deaths annually from GI bleeding.¹¹ A risk analysis¹² based on a retrospective case-control survey of emergency admissions for upper GI disease in two United Kingdom general hospitals provided useful estimates of the frequency of serious GI complications from NSAIDs.¹³ In people taking NSAIDs, the 1-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647 (Table 1). In addition to age, prednisone use, disability level, and previous NSAID-induced GI symptoms are risk factors for GI bleeding.

Table 1. One year risk of GI bleeding due to NSAID

Age range (years)	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
<i>Risk in any one year is 1 in:</i>		
16-45	2100	12,353
45-64	646	3800
65-74	570	3353
> 75	110	647
Data are from Blower, ¹³ recalculated in Moore ¹² and in Bandolier ¹⁴		

NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. Theoretically, an NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. Appendix B¹⁵ summarizes the NSAIDs and their selectivity based on assay studies (done in the laboratory instead of in living patients). The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results, and assay method may not reliably predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs.

In addition to their propensity to cause GI bleeding, NSAIDs are also associated with adverse effects on blood pressure, renal function, and fluid retention. Mechanisms may involve attenuation of prostaglandin-mediated vasodilation, promotion of sodium and water retention, increased vascular resistance, and increased renal endothelin-1 synthesis.¹⁶⁻¹⁸

An association between selective COX-2 inhibitors and increased rates of myocardial infarction was first observed in the large, pivotal Vioxx Gastrointestinal Outcomes Research (VIGOR) trial comparing high-dose rofecoxib (50 mg) to naproxen 1000 mg.¹⁹ Reasons for the increase in thromboembolic cardiovascular event risk are complex and not completely understood, but may be related in part to suppression of endothelial-derived prostaglandin I₂ formation by selective COX-2 inhibition, in the setting of unaffected platelet production of pro-thrombotic COX-1 mediated thromboxane A₂.²⁰ Blood pressure elevations associated with COX-2 inhibitors may also play a role in increasing cardiovascular risk.²¹ On September 30, 2004, rofecoxib was withdrawn from the market after a long-term polyp prevention trial found an increased risk of myocardial infarction compared with placebo.²² On December 9, 2004, the US Food and Drug Administration issued a black-box warning for valdecoxib for life-threatening skin reactions and increased cardiovascular risk. This drug was subsequently also withdrawn voluntarily by the manufacturer.²³

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, anti-pyretic, and anti-inflammatory effects.²⁴ It is thought to be the most consumed medicinal drug in the world. Like the non-aspirin NSAIDs, aspirin's effects are due to blockade of cyclo-oxygenases. However, an important distinction between aspirin and non-aspirin NSAIDs is that aspirin also induces irreversible functional defects in platelets (although non-aspirin NSAIDs also have effects on platelet aggregation, they are short-lived). Because of these antiplatelet effects, low-dose aspirin is also used prophylactically to reduce the risk of thrombotic events.²⁵ However, even at doses of 325 mg daily or lower, the potential cardiovascular benefits must be balanced against dose-dependent risk of aspirin-induced adverse GI events. Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. However, salsalate is considered a relatively weak inhibitor of cyclo-oxygenases.²⁶

Acetaminophen (also known as paracetamol) is an anti-pyretic and analgesic medication that

is not thought to have significant anti-inflammatory properties. Although its mechanism of inducing analgesia is still not completely understood, it is thought to work in part by indirectly decreasing production of prostaglandins through inhibitory effects involving COX-2.^{16, 27} Acetaminophen is frequently recommended as a first line agent for osteoarthritis and other pain conditions because of its perceived favorable safety profile—particularly with regard to ulcer risk.²⁸

Chondroitin sulfate and glucosamine sulfate are natural compounds found in cartilage. Both are marketed to patients who have osteoarthritis. The precise mechanisms of action are unknown, but may involve promoting maintenance and repair of cartilage. Glucosamine, for example, has been shown to increase proteoglycan synthesis.²⁹ In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the U.S., by contrast, glucosamine and chondroitin are considered dietary supplements and are not regulated as pharmaceuticals. Adequate standardization of glucosamine and chondroitin preparations is a significant concern. It has been shown that the actual content often varies substantially from what is stated on the label.³⁰ Such inconsistencies may have implications on estimates of efficacy and safety for different commercial preparations.

Topical administration of NSAIDs could theoretically result in local analgesic and anti-inflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.³¹ Experimental studies indicate that topical administration is associated with substantially higher concentrations of NSAIDs in soft tissue (particularly meniscus and cartilage) and lower peak plasma concentrations compared with oral administration.⁶ For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and anti-inflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.³¹ Superior *in vivo* permeability characteristics, however, may not predict clinical effectiveness.

In contrast to topical NSAIDs, whose mechanism of action involves inhibition of cyclooxygenase, topical rubefacients are thought to relieve pain through counter irritation.^{6, 32} Although the mechanism of action of topical preparations containing salicylate esters is unclear, they are now usually classified as rubefacients rather than topical NSAIDs because they may not work via inhibition of cyclo-oxygenase.^{6, 33} Capsaicin, which is also often classified as a rubefacient, is derived from the hot chili pepper (*Capsicum* species). It is applied topically and thought to work by stimulating the release of substance P and other neuropeptides from sensory nerve endings.³⁴ Although this release can initially lead to burning and pain, analgesia occurs after repeated and continued application, as substance P becomes depleted. Although a wide variety of other rubefacients are available, only topical salicylates and capsaicin were included in this review.

The purpose of this report was to assess the comparative efficacy and safety of non-opioid oral medications (selective and non-selective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Scope and Key Questions

1. What are the comparative benefits and harms of treating osteoarthritis

with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: This question addresses the therapeutic benefits of long-term use for the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including use for other labeled indications such as the treatment of rheumatoid arthritis.)*

Oral NSAIDs include:

- aspirin
- celecoxib
- choline magnesium trisalicylate
- diclofenac
- diflunisal
- etodolac
- etoricoxib*
- fenoprofen
- flurbiprofen
- ibuprofen
- indomethacin
- ketoprofen
- ketoprofen ER
- ketorolac
- lumiracoxib*
- meclofenamate sodium
- mefenamic acid
- meloxicam
- nabumetone
- naproxen
- oxaprozin
- piroxicam
- rofecoxib*
- salsalate
- sulindac
- tenoxicam*
- tiaprofenic acid*
- tolmetin
- valdecoxib*

* These drugs are currently not approved (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) for use in the United States by the FDA or have been withdrawn from the market (rofecoxib and valdecoxib)

Other oral agents include acetaminophen, chondroitin, and glucosamine. See Appendix A for a detailed listing of pharmacokinetics, indications, and recommended dosing information for all included drugs. Appendix C shows low, medium and high doses for the more commonly used NSAIDs.

For this report, we defined the terms “selective NSAID” or “COX-2 selective NSAID” as drugs in the “coxib” class (e.g. celecoxib, rofecoxib, and valdecoxib). We grouped etodolac, nabumetone, and meloxicam into a separate category that we referred to as “partially selective NSAIDs,” to explore how in vitro differences in COX-2 selectivity might translate into clinical differences in safety. The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined “non-aspirin, non-selective NSAIDs” or simply “non-selective NSAIDs” as all other NSAIDs. We included evidence on the efficacy and safety of the COX-2 inhibitor rofecoxib, even though it is no longer available in the U.S., because it was the first drug to be associated with cardiovascular risks and therefore provides important historical context and illustrates important issues to consider when evaluating the risks and benefits of selective and non-selective NSAIDs. For other COX-2 inhibitors not approved by the FDA for use in the U.S.

(lumiracoxib and etoricoxib) or withdrawn from the market (valdecoxib), we focused only on evidence regarding long-term, serious GI and CV adverse events, which is likely to be the most important factor driving future decisions regarding their use.

“Benefits” include relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales:³⁵

Visual analogue scale (VAS): Using VAS, patients indicate their level of pain, function, or other outcome by marking a scale labeled with numbers (such as 0 to 100) or descriptions (such as “none” to “worst pain I’ve ever had”). An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient’s subjective experience of pain. This poses a challenge in objectively comparing different patients’ scores, or even different scores from the same patient.

Categorical pain scales consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose among categories that may not accurately describe their pain. A variety of disease-specific and non-specific scales are used to assess these outcomes in patients with osteoarthritis. Commonly used categorical pain scales include:

- The *Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*, a 24-item, disease-specific questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.³⁶
- The *Medical Outcomes Short Form-36 (SF-36)* health survey, a commonly used general instrument for measuring health-related quality of life across different diseases.³⁷
- *Patient Global Assessment of Disease Status* and *Investigator Global Assessment of Disease Status*. The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or categorical scale.
- *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.

Another method for measuring outcomes is classifying patients dichotomously as “responders” or “non-responders.” Responders are often defined as patients with at least a 50% improvement in pain or function. The *Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria*, for example, were developed through a consensus process and classifies patients as responders if they meet specific pre-defined criteria ($\geq 50\%$ improvement in pain or function that was ≥ 20 mm on a 100 mm VAS, or a $\geq 20\%$ improvement in at least two of pain, function, or patient global assessment that was ≥ 10 mm on a 100 mm VAS).³⁸

“Harms” include tolerability (not having to stop the drug due to adverse effects); cardiovascular, hepato-, renal, and gastrointestinal toxicity; and increased risk for hospitalizations, drug interactions, and death. For gastrointestinal toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric

outlet obstruction, though we also evaluated other gastrointestinal side effects (such as nausea, dyspepsia, and gastrointestinal tolerability). We only considered rates of endoscopic ulcers when data on clinical ulcer complications were incomplete or not available.

2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?

- Demographic subgroups include age, sex, and race.
- Co-existing diseases include hypertension, edema, ischemic heart disease, heart failure, PUD, and history of previous bleeding due to NSAIDs.
- Concomitant medication use includes anticoagulants and aspirin.

3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors?

4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?

Topical preparations include:

- Capsaicin
- Diclofenac
- Ibuprofen
- Ketoprofen
- other NSAIDs
- salicylates

Chapter 2. Methods

Topic Development

The topic for this report was nominated in a public process. The key questions were developed by investigators from the Oregon EPC with input from a Technical Expert Panel (TEP) formed for this project. Contacted via teleconference, the TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. Results from previously conducted meta-analyses and systematic reviews on these topics were sought and used where appropriate and updated when necessary. To identify systematic reviews, in addition to MEDLINE, we searched the Cochrane Database of Systematic Reviews and the websites of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Bandolier, and the NHA Health Technology Assessment Programme.

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews (through 3rd Quarter 2005) the Cochrane Central Register of Controlled Trials (through 3rd Quarter 2005) and Ovid @MEDLINE (1966- July, 2005.) We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis (see Appendix D for the complete search strategy). Other sources include reference lists of review articles and unpublished materials from the US Food and Drug Administration (FDA). Pharmaceutical manufacturers were invited to submit scientific information packets, including citations if applicable. All 2,665 citations from these sources were imported into an electronic database (EndNote® 9.0) and considered for inclusion.

Study Selection

Systematic reviews and controlled trials pertinent to the key questions were included. We retrieved any blinded or open, parallel or crossover randomized controlled trial that compared one included drug to another, another active comparator, or placebo. We also included cohort and case-control studies with at least 1,000 cases or participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.

Data Extraction

The following data were extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), method of outcome ascertainment if available, and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if available.

Quality Assessment

Assessing Research Quality

We assessed the internal validity (quality) of systematic reviews and randomized trials based on the predefined criteria listed in Appendix E. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).³⁹ We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix E) assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, reported adequate detail of included studies, and used appropriate methods to synthesize the evidence. We included systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we considered this a methodological shortcoming.

For assessing the internal validity of observational studies, we evaluated whether they used nonbiased selection methods; whether rates of loss to follow-up were acceptable; whether pre-defined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal quality rating methods.⁴⁰ We therefore did not use a formal scoring system to rate the quality of the observational studies included in this review, but noted methodological deficiencies in any of the above areas when present.

Assessing Research Applicability

The applicability of trials and other studies was assessed based on whether the publication

adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the sponsor.

Rating a Body of Evidence

Overall quality ratings for an individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

We assessed the overall strength of evidence for a body of literature about a particular key question, by examining the type, number and quality of studies; the strength of association; the consistency of results within and between study designs; and the possibility for publication bias. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered “good-quality.”) For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

Data Synthesis

Effectiveness Versus Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes of most importance to patients, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of successful treatment, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales. Further discussion of these issues is available at <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

Data Presentation

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. We also performed two quantitative analyses for this review. An important limitation of observational studies of NSAIDs is that none simultaneously assessed the risk for

serious cardiac and GI events. We therefore re-analyzed data from a set of observational studies that reported rates of three different serious adverse events in the same population. We assumed that the adverse events occurred independently and that the logarithm of the rate ratios was distributed normally. After estimating the effect (number of events prevented or caused) for each of the three adverse events, we estimated the net effects on all three serious adverse events using Monte Carlo simulation.

We also pooled clinical success rates and withdrawal due to adverse events from head-to-head trials of topical versus oral NSAIDs using a random effects model (Dersimonian-Laird method, using RevMan® statistical software). We performed standard chi-square tests for heterogeneity. Because only four trials were available for pooling, we did not attempt meta-regression analyses to evaluate potential sources of heterogeneity.

Chapter 3. Results

Overview

Searches identified 2,789 publications: 1,522 from the Cochrane Central Register of Controlled Trials, 68 from the Cochrane Database of Systematic Reviews, 1015 from MEDLINE and 184 from the combination of other sources listed above. There were also 59 studies not previously reviewed for inclusion that were suggested through peer review or public comment or published after the searches were conducted. Following application of inclusion criteria, 351 publications were included in this review.

Key Question 1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

Benefits: Effectiveness and Efficacy

Effectiveness Studies

No controlled clinical trials of COX-2 inhibitors and/or NSAIDs met all major criteria for an effectiveness study (conducted in mainly primary care or office-based settings, used broad enrollment criteria, and evaluated longer-term, “real-life” outcomes).

Efficacy

Non-selective NSAIDs vs. other NSAIDs. Several good-quality systematic reviews by the Cochrane Collaboration evaluated trials that compared non-aspirin NSAIDs for OA of the hip (trials published through 1994),⁴¹ for OA of the back (through 1998),¹⁰ and for OA of the knee (through 1997).⁴² These reviews found no clear differences among non-aspirin and primarily non-selective NSAIDs in efficacy. There were also no differences between diclofenac and sustained-release etodolac in patients with OA of the knee⁴³ or between piroxicam and standard formulation etodolac in patients with OA of the knee or hip⁴⁴ in two trials published subsequent to the Cochrane reviews.

Nabumetone was similar in efficacy to the non-selective NSAIDs diclofenac SR⁴⁵ and etodolac⁴⁶ in two 4-week trials, as reported in the Cochrane review of OA of the knee.⁴²

No studies of meloxicam, salsalate, or aspirin were included in any Cochrane reviews. We identified nine double-blinded trials of meloxicam 7.5 mg, 15 mg, and 25 mg versus other NSAIDs and found no clear or consistent differences in efficacy.⁴⁷⁻⁵⁵ In two of the trials, however, patients taking non-selective NSAIDs were significantly less likely to withdraw due to

lack of efficacy than patients taking meloxicam.^{49, 54}

In the only head-to-head trial of salsalate (3 g) in patients with OA, efficacy was similar to that of 3.6 g soluble aspirin after two weeks of treatment.⁵⁶

Celecoxib vs. non-selective NSAIDs. Celecoxib and non-selective NSAIDs were associated with similar decreases in symptom severity and improvements in functional capacity (PGA, WOMAC) after 6- to 24-weeks in five published trials of patients with primarily OA.⁵⁷⁻⁶⁰

A good-quality systematic review funded by the makers of celecoxib reached similar conclusions based on data from published and unpublished trials of at least 12 weeks' duration in patients with either OA or RA.⁶¹

Using an alternative endpoint, a more recent systematic review (published in 2005) with access to all unpublished manufacturer-held clinical trial reports reached slightly different conclusions about the relative efficacy of celecoxib and NSAIDs.⁶² Moore et al meta-analyzed data from 31 primarily short-term (≤ 12 weeks) trials and concluded that celecoxib at dose of 200-400 mg was associated with slightly higher rates of withdrawals due to lack of efficacy compared to non-selective NSAIDs (RR 1.1; 95% CI 1.02, 1.23). CLASS remains the pivotal, long-term study (6 to 13 months) of celecoxib in patients with rheumatoid and osteoarthritis. It randomized a total of 7,968 patients to celecoxib or the non-selective NSAIDs ibuprofen or diclofenac. A higher proportion of non-selective NSAID patients withdrew due to lack of efficacy (14.8% vs. 12.6%, $p=0.005$). However, CLASS focused on assessment of adverse events rather than efficacy, and other efficacy results were reported. SUCCESS-1, a shorter (12-week), double-blind, randomized trial of 13,274 patients with osteoarthritis, found no clinically meaningful differences between celecoxib 100 mg or 200 mg twice daily and the non-selective NSAIDs diclofenac or naproxen.⁶³

Rofecoxib vs. non-selective NSAIDs. We were unable to determine whether all manufacturer-sponsored trials of rofecoxib versus NSAIDs have been published.^{19, 64-76} All but one of the trials included osteoarthritis patients, and all but two^{70, 72} were supported by the manufacturer of rofecoxib. All but two of the OA trials^{73, 76} have been previously analyzed in a good-quality Cochrane review.⁷⁷ Conclusions of the Cochrane review are consistent with our findings that there were no consistent differences between rofecoxib and non-selective NSAIDs in efficacy for OA. In addition, a pivotal, good-quality trial (VIGOR) and a good-quality Cochrane review found rofecoxib equivalent to naproxen in efficacy for rheumatoid arthritis.^{19, 78}

Valdecoxib vs. non-selective NSAIDs. In clinical trials submitted to the FDA, valdecoxib was as effective as ibuprofen (800 mg 3 times/day), diclofenac (75 mg twice daily), and naproxen (500 mg twice daily) in treating osteoarthritis symptoms. Published trials found no difference in efficacy between valdecoxib and naproxen⁷⁹⁻⁸¹ or ibuprofen or diclofenac.⁸² A fifth trial found no difference in efficacy between valdecoxib 20-40 mg and slow-release diclofenac 75 mg in treating rheumatoid arthritis.⁸³

Comparisons between selective COX-2 inhibitors. We found six published randomized, multicenter, fair-to-good quality trials that directly compared COX-2 inhibitors for osteoarthritis of the knee.⁸⁴⁻⁸⁹ Pharmaceutical manufacturers were reported as funding sources in all but one study.⁸⁸ This small ($N=30$), short-term (7 days), fair-quality trial found that rofecoxib 25 mg and celecoxib 200 mg had similar effects on patients' pain intensity, 3-hour pain relief, global

assessment of efficacy and rescue medication use.⁸⁸ Two trials of higher-risk osteoarthritic patients with hypertension (both funded by the maker of celecoxib) found no differences in efficacy between rofecoxib 25 mg and celecoxib 200 mg daily, but reported a higher rate of adverse events with rofecoxib.^{84, 85}

The remaining three trials appeared to enroll patients with similar demographics and baseline levels of pain and were more homogeneous in design (see table below).^{86, 87, 89} All compared rofecoxib 25 mg qd and celecoxib 200 mg qd in patients with flare-ups of chronic osteoarthritis of the knee and were 6 weeks in duration. One trial, funded by the manufacturer of celecoxib, found no difference in efficacy between rofecoxib and celecoxib, but a higher rate of adverse events with rofecoxib.⁸⁶ Another (VACT, or *Vioxx Acetaminophen Celecoxib Trial*)⁸⁷ trial, funded by the manufacturer of rofecoxib, found rofecoxib more effective than celecoxib, with no differences in rates of adverse effects. The most recent study, funded by the maker of celecoxib,⁸⁹ found no difference in either efficacy or adverse effects between celecoxib and rofecoxib.

Table 2. Comparison of rofecoxib and celecoxib in flare-ups of chronic osteoarthritis of the knee

Characteristic	McKenna ⁸⁶	Geba ⁸⁷	Gibofsky ⁸⁹
Rofecoxib 25mg (n)	59	95	190
Celecoxib 200mg (n)	60	97	189
Aspirin 325 qd permitted	Yes	No	Yes
Mean age	62	62.6	62.9
Mean osteoarthritis duration	10.5 years	10 years	9 years
Percent white	80%	85%	NR
Baseline pain on walking (score)	72	72	68
Discontinued trial by 6 wks:			
Rofecoxib 25mg	16%	19%	15%
Celecoxib 200mg	22%	17%	16%

All three trials were probably adequately randomized and blinded, and didn't have statistically significant differences in baseline characteristics. Gibofsky and colleagues hypothesized that neither McKenna nor Geba were powered sufficiently to measure differences between celecoxib and rofecoxib. Gibofsky viewed the McKenna study as being powered only to compare active treatments with placebo and the Geba study as powered to compare rofecoxib with acetaminophen. Therefore, Gibofsky, and colleagues set out to conduct a study powered to compare celecoxib and rofecoxib, with a sample size based on results of the McKenna study.

Efficacy results are summarized in Table 3 below. Mean changes in WOMAC VAS score for Walking Pain were similar for celecoxib 200 mg and rofecoxib 25 mg across trials. In the Geba trial, rofecoxib was associated with significantly greater mean reductions than celecoxib on VAS scores for WOMAC Rest Pain and Night Pain and a similar mean reduction in Morning Stiffness. WOMAC Composite Score results from Geba and Gibofsky were conflicting. In the Gibofsky trial, there were no differences, but in the Geba trial, there were significant differences favoring rofecoxib for mean changes in the WOMAC pain (7 points) and stiffness (8 points) subscales. However, an analysis of data from randomized trials estimated that the minimal perceptible improvement for each WOMAC scale was a difference of 11 mm.⁹⁰

Table 3. Head to head efficacy comparisons at 6 weeks (mean change from baseline)

	WOMAC VAS Scores					WOMAC Composite Subscales			
	Walking pain	Rest pain	Morning stiffness	Night pain	Arthritis pain	Pain	Stiffness	Function	Total
Geba⁸⁷									
Rofecoxib	-42	-31.1*	-36.2	-32.7**	nr	-35.4*	-35*	-29.7	-26
Celecoxib	-36.2	-23.4	-29.1	-22.6	nr	-28.6	-27.9	-24.9	-26
McKenna⁸⁶									
Rofecoxib	-38	nr	nr	nr	-40	nr	nr	nr	nr
Celecoxib	-38	nr	nr	nr	-39	nr	nr	nr	nr
Gibofsky⁸⁹									
Rofecoxib	-29.2	nr	nr	nr	nr	-42.6	-34.7	-35.5	-20.1
Celecoxib	-31.5	nr	nr	nr	nr	-42.0	-36.7	-37.9	-22.1

*p≤0.05; **p<0.001; nr=not reported

Safety: Serious Gastrointestinal and Cardiovascular Events

Rofecoxib and Celecoxib: GI and CV Safety in CLASS and VIGOR

GI Safety

Two pivotal studies were large enough to evaluate serious complications of peptic ulcer disease (bleeding, perforations, obstruction) as a primary endpoint in average-risk patients (those without a recent UGI bleed). The VIGOR trial¹⁹ evaluated rofecoxib versus naproxen and the CLASS trials⁶⁰ evaluated celecoxib versus ibuprofen and diclofenac.

VIGOR (Vioxx Gastrointestinal Outcomes Research) Trial. VIGOR, a randomized, double-blind trial, compared twice the highest recommended dose of rofecoxib (50 mg daily) to naproxen 500 mg twice a day in 8,076 patients with rheumatoid arthritis. VIGOR found a statistically significant reduction in complicated upper GI events (defined as perforation, obstruction, or severe upper gastrointestinal bleeding. During a median follow-up of 9 months, the rates of confirmed upper gastrointestinal events were 3.0% vs. 1.4% (NNT to prevent one event 62), and the rates of complicated, confirmed upper gastrointestinal events were 0.9% vs. 0.4% (NNT 192).

VIGOR met all but one of the criteria for a good-quality study. The one weakness was the varying duration of exposure among study participants. The duration of VIGOR was designed to be both time and event driven, so that the trial would terminate after a minimum of 120 patients experienced clinical upper GI events (or 40 patients experienced complicated upper GI events) and for at least 6 months after randomization of the last patient enrolled. Because patients were enrolled over a 6-month period, patients in VIGOR were followed for varying lengths of time. The longest time a patient could have remained in the study was 13 months, but half of the patients were followed for 9 months or less, and only about 1,000 patients (13%) were followed for longer than 10 months. By 13 months, about 29% of the subjects had discontinued the study drugs. Similar proportions discontinued naproxen or rofecoxib because of an adverse event (naproxen—16.1%, rofecoxib—16.4%).

In 2003, the VIGOR investigators published a *post hoc* analysis of lower GI events, defined

as bleeding with a 2 g/dL drop in hemoglobin or hospitalization, or hospitalization for perforation, ulceration, diverticulitis, or obstruction.⁹¹ There were 11 events in the rofecoxib group and 24 events in the naproxen group (0.41 versus 0.89 per 100 patient-years; RR 0.46, 95% CI 0.22 to 0.93). The absolute risk difference (per 100 patient-years) was -0.48 (95% CI -0.91 to -0.05), with a NNT of 208. When the investigators combined the analysis of lower GI events with previously reported results on upper GI complications (0.6 with rofecoxib versus 1.4 with naproxen per 100 patient-years⁹²), the rates of all serious GI events were 0.96 for rofecoxib and 2.26 per 100 patient-years for naproxen (relative risk 0.43, 95% CI 0.27 to 0.67, NNT 77).

CLASS (Celecoxib Long-term Arthritis Safety Study.) CLASS was designed as two trials with separate patient recruitment and randomization procedures: one compared celecoxib 400 mg twice a day with ibuprofen 800 mg three times a day, and the other compared celecoxib 400 mg twice a day with diclofenac 75 mg twice a day.⁶⁰ Because the FDA was concerned that selective COX-2 inhibitors could interfere with the benefits of COX-2 in ulcer healing and lead to a long term increase in GI complications without warning symptoms, the pre-specified primary outcome was “ulcer-related complications.”⁹³ Another pre-specified outcome was ulcer related complications plus symptomatic ulcers. The planned maximum duration of the trials were 15 and 12 months, respectively, or until at least 20 ulcer-related complications occurred in each trial, or 45 in both trials combined.⁹⁴ The protocols stated that celecoxib would be claimed to be different from traditional NSAIDs only if there were statistically significant differences between celecoxib and each of the comparators, as well as between celecoxib versus the comparator groups combined.

The CLASS trials were stopped early after the predefined threshold of ulcer complications occurred. However, the analysis and reporting of the results as presented in the main publication in JAMA were in part incomplete and differed in some ways from the protocols. The JAMA article reported truncated 6-month results even though the median duration of follow-up was 9 months (range 6 to 13 months), and combined the ibuprofen and diclofenac results without reporting the results of the two trials separately.⁶⁰ Subsequently, additional details of the study have been made public on the FDA web site⁹⁴ and have been extensively analyzed. The findings of the FDA analysis suggest that the published results of CLASS are, in part, misleading because they appear to selectively report results at the point in time at which celecoxib was most effective.⁹⁵⁻⁹⁷

There were 3,987 subjects randomized to celecoxib and 3,981 subjects randomized to non-selective NSAIDs in the CLASS trials. For the combined outcome of ulcer complications or symptomatic ulcers, the JAMA article reported that patients on celecoxib experienced fewer GI complications compared with patients in the combined NSAID groups (32/3987 versus 51/3981, annualized incidence rates 2.08% vs. 3.54%, $p=0.02$),⁶⁰ while the rate of complicated ulcers alone was not significantly different (13/3987 vs. 22/3981, annualized incidence rates 0.76% vs. 1.45%, $p=0.09$). However, by 12 months, according to FDA documents (see Table 14, FDA Medical Officer Review)⁹⁴ there was no longer a trend favoring celecoxib for the primary outcome of complicated ulcers. There were 17/3987 events in the celecoxib group (0.43%) versus 21/3981 (0.53%) in the NSAID groups combined.⁹⁴ This difference was not statistically significant (relative risk 1.10, 95% CI 0.47 to 2.58^{97,98}, also see Figure 4, Scheiman review⁹⁹). For the individual comparisons between celecoxib and ibuprofen or diclofenac, which were not reported in the JAMA article, there was no difference in the rate of ulcer complications at either 6 months or at the end of follow-up.⁹⁷ For the outcome of ulcer complications or symptomatic ulcers, celecoxib was superior to ibuprofen, but not to diclofenac at either 6 months or at the end

of follow-up.⁹⁷

Authors of CLASS have not completely explained the reasons for selective reporting of results, though they contend that combining the two trials and reporting ulcer complications plus symptomatic ulcers as a primary outcome were permitted by the protocols.^{100, 101} However, reporting only combined results appears to obscure differences between the results for the two comparator drugs.⁹⁶ The investigators' main argument for reporting truncated data is that results after 6 months were not interpretable because of high and differential rates of drop-outs due to symptomatic ulcers, which could have biased results against celecoxib because of depletion of high-risk patients in the non-selective NSAID arms.^{100, 101} On closer inspection, however, this rationale appears flawed, as neither symptomatic ulcers nor gastrointestinal symptoms predicted ulcer complications.⁹⁶ Furthermore, simply truncating data is not considered an acceptable method for resolving issues related to high drop-out rates.

Twenty per cent of the patients in the CLASS trial took aspirin in addition to their study drug. When patients taking aspirin were excluded from the analysis, there were fewer confirmed serious ulcer complications in the celecoxib group than in the ibuprofen group ($p=0.03$).^{94, 97} However, serious ulcer complications for celecoxib and diclofenac were equivalent even when patients taking aspirin were excluded from the analysis.

Changes in hemoglobin or hematocrit were not a primary outcome of CLASS and were not reported in the main JAMA publication. However, rates of significant hemoglobin (>2 g/dL) and/or hematocrit drops (≥ 0.10), a surrogate marker for GI blood loss, are available from the FDA Medical Officer Review.⁹⁴ Over the entire study period, patients randomized to celecoxib were significantly less likely to experience declines in these laboratory parameters (87/3701 or 2.4%) relative to patients randomized to either diclofenac (82/1849 or 4.4%) or ibuprofen (102/1802, 5.7%). Celecoxib was also superior when patients were stratified according to aspirin use (4.1% vs. 6.9% and 7.5%) or non-use (1.9% vs. 3.7% and 5.2%). However, the significance of these findings is unclear as they were not associated with differences in clinically relevant outcomes (such as rates of MI, angina, or congestive heart failure).

In summary, the CLASS trials did not demonstrate a statistically significant advantage over either diclofenac or ibuprofen for the primary endpoint of complicated ulcers for all patients enrolled over the full duration of follow-up. Celecoxib appeared superior to ibuprofen, but not diclofenac, in a subgroup of subjects not taking aspirin. In its decision regarding labeling for celecoxib, the FDA agreed with its Advisory Committee recommendations that CLASS did not demonstrate a safety advantage in upper gastrointestinal safety for celecoxib compared with either ibuprofen or diclofenac.¹⁰²

Comparison between VIGOR and CLASS. There are several possible reasons why rofecoxib (VIGOR), but not celecoxib (CLASS), significantly reduced ulcer complications. First, patient populations and study designs differed. VIGOR included patients aged 50 or older with rheumatoid arthritis, while CLASS had a broader age range of patients with either osteoarthritis or rheumatoid arthritis. VIGOR also prohibited the use of aspirin while CLASS did not. However, the rate of ulcers in the patients taking a control drug was almost three times as high in VIGOR as in CLASS, although rates of ulcer complications were similar. In addition, VIGOR compared rofecoxib to naproxen and CLASS compared celecoxib to diclofenac and ibuprofen. This could have affected the results if the non-selective comparator NSAIDs are associated with differential risk of ulcers. Finally, it is possible that rofecoxib, which has greater COX-2 selectivity, is truly more gastroprotective than celecoxib.

CV risk in VIGOR. Findings from the VIGOR trial raised concerns that the putative GI safety benefits of COX-2 selective NSAIDs relative to non-selective NSAIDs may have come at the expense of increased cardiovascular events. The main publication of VIGOR¹⁹ reported that “the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.” This corresponds to one additional heart attack for every 333 patients treated with rofecoxib instead of with naproxen. A re-analysis of VIGOR with three additional myocardial infarctions not included in the results originally submitted for journal publication estimated a relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen among all patients, and 3.00 (95% CI 0.91 to 12.78) among patients in whom aspirin was not indicated.¹⁰³ For patients who had indications for aspirin, 8 MIs occurred during 105 person-years of exposure to rofecoxib, compared with no MIs during 102 person-years of exposure to naproxen. Blinded adjudication of the VIGOR trial data classified 45/4047 (one in every 90) rofecoxib patients and 19/4029 (one in 212) naproxen patients as having serious thrombotic events (heart attack, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest, and sudden death).¹⁰⁴ This corresponds to one additional serious thrombotic event for every 156 patients taking rofecoxib.

CV risk in CLASS. The original publication of the CLASS trials, using 6-month data, reported that celecoxib had no effect on the rate of myocardial infarction or for any cardiovascular event (stroke, myocardial infarction, or angina) compared with diclofenac and ibuprofen.⁶⁰ The number of myocardial infarctions was 10/3987 (0.3%) with celecoxib versus 11/3981 (0.3%) with the non-selective NSAIDs. The full CLASS data on thrombotic events were analyzed in more detail by White and colleagues,¹⁰⁵ who also found no differences in the rates of any significant cardiovascular event for the overall sample or for the subgroup who did not use aspirin. For the overall sample, myocardial infarctions occurred in 19/3987 (0.5%) of patients on celecoxib and 13 (0.3%) on diclofenac or ibuprofen. In fact, more detail about the design of the CLASS trials is necessary to judge the validity and generalizability of these results. In particular, reporting of longer-term data is important because 6 months of exposure to celecoxib may not be enough time to assess cardiovascular risk. At 8 months in the VIGOR trial there was no significant difference between rofecoxib and naproxen in the cumulative incidence of events. From 8 to 12 months, differences in the incidence of myocardial infarction between rofecoxib and naproxen became apparent (Figure 1 of Mukherjee¹⁰⁶). This observation could be due to increased power due to a larger number of events with longer follow-up, or in part to a duration-dependent increase in risk. Based on the pattern observed in VIGOR, if celecoxib is associated with an increased risk of cardiovascular events, it may not be seen until 10 or 12 months of followup. In the VIGOR trial, 2,140 subjects, about one-fourth of the original sample, were available for 10 months of followup, and 1,045 were available for 12 months. In the CLASS trials, 2,770 subjects, about one-third of the original sample, had at least 9 months of follow-up, and 1,126 had at least 12 months of follow-up, suggesting that an analysis should have been able to detect an increased risk of cardiovascular events similar to that observed in VIGOR, if it was present (see Table 4, FDA Medical Officer Review⁹⁴).

White and colleagues argue that their meta-analysis shows that celecoxib is safer than rofecoxib.¹⁰⁵ To support their argument, they note that the annualized rate of all cardiovascular

thromboembolic events in the naproxen group in the VIGOR trial and the non-aspirin celecoxib users in the CLASS trial were similar. However, this comparison of rates across the VIGOR and CLASS studies is imprecise. After 8 months, about 0.4% of naproxen patients had experienced an event in VIGOR, compared to about 0.8% of non-aspirin celecoxib users in CLASS. It is not clear whether or not this is a statistically significant difference. By contrast, Mukherjee and colleagues suggested that the selective NSAIDs as a class might be associated with an increased risk of myocardial infarction because the 0.8% rate of myocardial infarction on celecoxib in the CLASS trials and the 0.74% rate on rofecoxib in VIGOR are both higher than the 0.52% rate observed in a meta-analysis¹⁰⁷ of patients receiving placebo in studies of aspirin prophylaxis.¹⁰⁶ In our opinion, all of these conclusions are unsubstantiated because they involve cross-trial and historical comparisons.

The importance of analyzing longer-term data and assessing dose effects are underscored by the results of the long-term Adenoma Prevention with Celecoxib (APC) trial in a different population—that of patients receiving celecoxib for colorectal polyp prevention.¹⁰⁸ This trial, which randomized patients to celecoxib versus placebo, was terminated after 33 months because of a higher rate of cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) in the celecoxib arms. According to Figure 1 in the main publication of this trial,¹⁰⁸ the difference in rates of events became most apparent only after twelve to eighteen months. There was also a non-significant increase in risk with higher compared to lower doses of celecoxib. Compared with placebo, the relative risk of cardiovascular events in patients randomized to celecoxib 400 mg twice daily was 3.4 (95% CI 1.4 to 8.3) compared to 2.5 (95% CI 1.0 to 6.3) in patients randomized to 200 mg twice daily.¹⁰⁸ Much of the increased risk was due to differences in rates of fatal or nonfatal myocardial infarctions, which occurred in 22/1356 (1.6%) of celecoxib users and 3/679 (0.4%) of patients on placebo.¹⁰⁹ On the other hand, data from PreSAP,¹¹⁰ another polyp prevention trial, and preliminary data from ADAPT,¹¹¹ an Alzheimer's prevention trial, found no significant increase in cardiovascular events with celecoxib 400 mg once daily (PreSAP, RR 1.3, 95% CI 0.6 to 2.6¹⁰⁹) or 200 mg twice daily (ADAPT) compared to placebo. However, the lack of an association could be due to insufficient power to detect a difference because of the small number of myocardial infarctions associated with celecoxib in these trials (2 in ADAPT¹¹² and 9 in PreSAP¹⁰⁹). Alternatively, the smaller relative risk in PreSAP relative to APC could be related to a higher placebo event rate in PreSAP (7.2 versus 3.4 per 1000 patient-years).¹⁰⁹ SUCCESS-I, a recently published, large (N=13,274) trial of osteoarthritis patients, also reported no significant difference in rates of cardiovascular thromboembolic events with celecoxib 100 mg or 200 mg twice daily versus diclofenac or naproxen (10 events or 0.55/100 patient-years in the combined celecoxib arms versus 1 event or 0.11/100 patient-years in the non-selective NSAID arms, p=0.11), but may have been too short in duration (12 weeks) and have recorded too few events to detect a difference.⁶³

Overall rate of serious adverse events in CLASS and VIGOR. One Canadian analysis used FDA materials to analyze the rates of serious adverse events, defined as death, hospitalization, or “any life-threatening event, or event leading to severe disability” in the CLASS and VIGOR trials.¹¹³ This measure combines the rates of serious upper GI complications (in which coxibs are expected to have an advantage over NSAIDs) with other serious adverse events. The numbers of all serious adverse events were drawn directly from FDA materials, pages 7 and 8 (rofecoxib¹¹⁴) and 57 (celecoxib⁹⁴).

In the Canadian re-analysis, shown in Table 4, the rates were calculated using the number of patients as the denominator. These simple rates are compared with the number of serious upper GI events, which constitute only about 10% of all serious adverse events (the two rightmost columns in the table). Using all serious adverse events as the criterion for “harm,” the number-needed-to-harm one person was 82 for celecoxib vs. diclofenac, 129 for celecoxib vs. ibuprofen, 100 for celecoxib vs. diclofenac and ibuprofen, and 65 for rofecoxib vs. naproxen. The Canadian authors also pooled the results for celecoxib and rofecoxib, assigning more weight to VIGOR, which had a longer duration than CLASS. In the pooled analysis, the number needed to harm was 78 for the selective COX-2 inhibitors versus non-selective NSAIDs and was statistically significant.

Table 4. Re-analysis of the CLASS and VIGOR Trials¹¹³

Trial	ALL SERIOUS ADVERSE EVENTS		SERIOUS UPPER GI EVENTS	
	Treatment	Control	Treatment	Control
CLASS ⁶⁰ (Celecoxib 400 mg)	270/3987 (6.8%)	230/3981 (5.8%)	20/3987 (0.5%)	24/3981 (0.6%)
VIGOR ¹⁹ (Rofecoxib 50 mg)	378/4047 (9.3%)*	315/4029 (7.8%)	16/4047 (0.4%)*	37/4029 (0.9%)

*statistically significant vs. control group.

For the VIGOR trial, the FDA calculated rates of serious adverse events in exactly the same manner as the Canadian investigators.¹¹⁴ The FDA analysis shows that the rates of each serious adverse event (except GI adverse events) were higher for rofecoxib than for naproxen. For the CLASS trials, the FDA used patient-years as the denominator instead of a simple proportion to calculate rates of serious adverse events.⁹⁴ This approach was used because the two trials that make up CLASS had different durations. In the FDA analysis, the rates of all serious adverse events combined were 11.6 per 100 patient-years for celecoxib; 10.3 per 100 patient-years for diclofenac, and 10.6 per 100 patient-years for ibuprofen, a difference that was not statistically significant.

In summary, the FDA data clearly show that these two coxibs, in doses higher than those commonly used in practice, do not reduce the overall rate of serious adverse events, and may have increased them. It should be noted, however, that not all serious adverse events are equal in importance to patients and physicians. A reduction in the rate of one kind of adverse event might be considered more important than an increase in another one.

Rofecoxib and Celecoxib: Further Analyses of CV Toxicity and GI Safety

The GI and CV risk profiles of celecoxib and rofecoxib relative to one another and to NSAIDs, placebo, or no treatment have also been assessed in numerous meta-analyses of randomized trials and observational studies. We were unable to obtain final results of one systematic review evaluating the GI safety associated with selective and non-selective NSAIDs in time to include it in this report.¹¹⁵ However, analyses of GI safety with celecoxib and rofecoxib in this systematic review were based on results from CLASS,⁶⁰ VIGOR,¹⁹ the then-unpublished SUCCESS-1 trial of celecoxib,¹¹⁶ and two previously published meta-analyses^{117, 118} (all included in this report).

Rofecoxib. VIGOR remains the only individual trial large enough to adequately assess rates of upper GI complications with rofecoxib and non-selective NSAIDs in patients with arthritis. However, the manufacturer of rofecoxib also sponsored a prospective meta-analysis of GI safety from eight smaller phase 2b/3 osteoarthritis trials (N=5425).¹¹⁸ It found the 12-month combined incidence of perforations, symptomatic ulcers, and upper GI bleeding significantly lower with rofecoxib compared to non-selective NSAIDs (1.3% vs. 1.8%, $P=0.046$; rate per 100 patient-years 1.33 vs. 2.60, RR 0.51, 95% CI 0.26 to 1.00). The rate of ulcer complications alone, however, was not reported. A Food and Drug administration review has been critical of several aspects of this meta-analysis.¹¹⁹ It notes that it is not clear how assiduously investigators of the trials adhered to the pre-specified protocols (for example, by not delivering the prespecified type of primary source material mandated in the original protocol), and that most (50 of 62) cases were unblinded before the adjudication process occurred. In addition, the FDA review suggests that simple pooling and comparisons of the rofecoxib and the non-selective NSAIDs outcomes may be misleading because study duration varied, different patient withdrawal criteria were applied, different diagnostic surveillance methods (including endoscopic surveillance in two trials) were employed, doses of rofecoxib varied, and different comparator NSAIDs were used. Rates of complicated ulcers at 12 weeks, for example, were substantially higher in patients on ibuprofen (1.12%) compared with diclofenac (0.19%). Further, combining symptomatic ulcers and ulcer complications may be less informative because the morbidity associated with ulcer complications is substantially higher than the morbidity associated with symptomatic ulcers. Data reported on the FDA web site (page 78) indicate that only six complicated ulcers in 3,357 patients on rofecoxib and five in 1,564 patients on non-selective NSAIDs (cumulative incidence at 12 months 0.45% vs. 0.55%) occurred; the difference was not statistically significant (relative risk using Cox proportional hazards model 0.51, 95% CI 0.16 to 1.69).¹¹⁹

An updated meta-analysis of 20 trials sponsored by the manufacturer of rofecoxib (excluding VIGOR) reported 0.21 vs. 0.45 confirmed complicated PUBs per 100 patient-years of exposure ($p=0.03$) among 10,026 subjects randomized to rofecoxib and 7,046 to non-selective NSAIDs. However, this meta-analysis was rated fair-quality because it did not evaluate the effects of study quality, duration of therapy, or dose (about 30% of patients received 12.5 mg of rofecoxib, about 50% received 25 mg, and about 10% received 50 mg).¹²⁰ With regard to duration of exposure, the results as presented in this study are somewhat misleading, as the rate of PUBs are reported as occurring over 24.8 months (last point in time at which there were >200 patients left in each treatment group), even though the median duration of exposure was only 3 months. Only one-quarter of the patients receiving rofecoxib had over 6 months of exposure.

The only randomized controlled trial evidence clearly demonstrating a lower risk of complicated ulcers with long-term use of rofecoxib compared with non-selective NSAIDs therefore comes from VIGOR, which evaluated a higher-than-conventional dose of 50 mg of rofecoxib. Although the most recent meta-analysis¹²⁰ reporting rates of complicated ulcers is consistent with VIGOR, its results appear primarily applicable to patients with shorter-term (<6 months) exposure to rofecoxib.

Celecoxib. One manufacturer-funded, fair-quality meta-analysis examined the endpoint of “UGI ulcer complications” in 14 RCTs of celecoxib (not including CLASS) versus placebo or non-selective NSAIDs (usually naproxen).¹²¹ The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The strength of this meta-analysis was that the endpoint—upper

GI bleeding with endoscopic findings of an ulcer or large erosion, perforation, or gastric outlet obstruction—was similar to those used in the VIGOR and CLASS trials. A Safety Committee adjudicated potential ulcer complications in a blinded manner. These endpoints were ascertained through a monitoring program that appears to have been superimposed on all of the trials; it is not clear how assiduously investigators complied with this program. Not all of the included trials have been published, and their quality was not assessed as part of the meta-analysis. In addition, like the meta-analysis of rofecoxib trials described above, results of the trials were simply pooled despite differences in dose of celecoxib, duration of therapy, or which comparator NSAID was used. In the 14 trials, there were 2 UGI ulcer complications among 6,376 patients in the celecoxib group (3 per 10,000), 9 among 2,768 in the NSAIDs group (33 per 10,000) and none in the placebo group (0/1,864). This corresponded to annual rates of two per 1,000 per year for celecoxib and about 17 per 1,000 per year for NSAIDs ($p=0.002$).

There are several possible reasons why the results of the meta-analysis differed from those of CLASS, which did not clearly show a decreased risk of UGI ulcer complications for celecoxib compared to diclofenac and ibuprofen. First, the incidence of serious ulcer complications in CLASS was much higher than in the trials included in the meta-analysis. In the CLASS trials, the annualized rate of serious ulcer complications was 7.6 per 1,000 per year for celecoxib and 14.5 per 1,000 per year for the two NSAIDs combined.⁶⁰ The nearly four-fold higher rate of ulcer complications in the CLASS trials compared to the other celecoxib trials could be due in part to enrollment of a higher-risk population, the use of concomitant medications, the dose of celecoxib evaluated, or other factors. In CLASS, for example, 21% of patients randomized to celecoxib were on aspirin and 30.6% on corticosteroids. By contrast, only 12.4% of patients in the meta-analysis were taking aspirin, and 13.5% were on corticosteroids.¹²¹ In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16.5% of celecoxib patients in the meta-analysis. Another potential explanatory factor is that the high dose of celecoxib used in CLASS—400 mg twice daily—was evaluated in only about 10% of the patients in the meta-analysis. It is possible that using higher doses of celecoxib could attenuate GI safety benefits because of incomplete COX-2 selectivity. Finally, different comparator NSAIDs could be associated with different risks of GI complications. In the meta-analysis, six trials ($N=6151$) compared celecoxib to naproxen versus only three trials ($N=2439$) that compared celecoxib to diclofenac or ibuprofen (the drugs evaluated in CLASS). Pooling data from trials evaluating different comparator NSAIDs could obscure differential effects on GI safety if they were present.

Moore, McQuay and others conducted a separate meta-analysis of celecoxib trials for osteoarthritis or rheumatoid arthritis, with funding from Pfizer and the Oxford Pain Relief Trust.⁶² The authors obtained a declaration from Pfizer that they had received information on all completed clinical trials of celecoxib and would be permitted to publish the results no matter what their findings showed. However, much of the data on which this meta-analysis was based remains inaccessible to the public. The unpublished data used in this meta-analysis add value in that they may help provide the most comprehensive and precise estimates of adverse events. However, although the meta-analysis methods appeared appropriate, it is impossible to verify whether the meta-analysis assessed validity appropriately, abstracted outcomes correctly, or otherwise confirm the reproducibility of the meta-analysis.

Moore and colleagues reviewed over 180,000 pages of company documents, which included detailed information on study methods. All 31 included trials were rated 5 out of 5 on the Jadad quality scale, and 16 out of 16 on an eight-item validity scale. Only two of the 31 trials were

longer than 12 weeks in duration. The meta-analysis found celecoxib associated with a lower risk of hemoglobin fall of 20 g/L or more (a marker for a significant GI bleed) (RR 0.72, 95% CI 0.56 to 0.92) and hematocrit fall of 5% or more (RR 0.78, 95% CI 0.69 to 0.89) compared with non-selective NSAIDs.⁶² Although the risk of complicated ulcers was not evaluated as a separate outcome, celecoxib was also associated with a lower risk of clinical ulcers and bleeds than non-selective NSAIDs in 18 trials (RR 0.61, 95% CI 0.46 to 0.81). When the analysis was limited to trials evaluating doses of 200 or 400 mg daily of celecoxib (in other words, excluding the results of CLASS), the benefit was more pronounced (RR 0.35, 95% CI 0.22 to 0.56).

The largest (N=13,274) randomized controlled trial (SUCCESS-1) of celecoxib (included in the Moore meta-analysis) assessed ulcer complications through 12 weeks.⁶³ It found that in patients with osteoarthritis, celecoxib was associated with a lower incidence of ulcer complications than naproxen or diclofenac (0.1% versus 0.8%, OR 7.02, 95% CI 1.46 to 33.8; p=0.008). Post hoc analysis indicated that non-aspirin users in the non-selective NSAID groups had a significantly higher risk of ulcer complications when compared to non-aspirin users in the celecoxib group (OR=12.05, 95% CI 1.45-100.09.) Among aspirin users, there was no statistically significant difference in the rates of ulcer complications for both NSAIDs and celecoxib.⁶³

Systematic Reviews and Meta-analyses of CV Toxicity

Rofecoxib. VIGOR and other randomized trials of rofecoxib have been extensively re-examined to further explore its cardiovascular risk profile. Many questions have been raised in response to the disparate findings of these analyses and a myriad of possible explanatory factors have been proposed.

Rofecoxib versus non-selective NSAIDs. In October 2001, a fair-quality meta-analysis published in *Circulation*¹²² by Konstam and colleagues reported pooled results from 23 rofecoxib Phase IIb through V trials sponsored by Merck. The investigators stratified results by patient group (rheumatoid arthritis, osteoarthritis, or Alzheimer's disease) and by control group (placebo, naproxen, or non-naproxen NSAID). The risk of cardiovascular events was 1.69 times higher for rofecoxib than for naproxen (95% CI 1.07 to 2.69), but was not elevated in trials comparing rofecoxib to non-naproxen NSAIDs (RR 0.79, 95% CI 0.40 to 1.55) (Table 5). The authors hypothesized that rofecoxib might have been an "innocent bystander" in the VIGOR trial. In other words, rather than rofecoxib increasing the rate of cardiovascular events, naproxen might have reduced it.

A problem with the Konstam analysis¹²² is that the non-naproxen and naproxen studies are not directly comparable. VIGOR, the only long-term COX-2 trial to demonstrate a significant reduction in serious GI events, used rofecoxib 50 mg, prohibited aspirin, and followed patients for 9 months. By contrast, some of the non-naproxen-controlled studies were 12 weeks or shorter in duration, permitted aspirin, or used lower doses of rofecoxib. The data presented in the meta-analysis are also inadequate to judge the quality of the included studies and how concomitant aspirin use, duration of treatment, or dose might have affected rates of cardiovascular events, as adjustment using individual patient risk factors was not performed.

A subsequent meta-analysis by Reicen and colleagues, also rated fair-quality, provided a more detailed analysis of eight phase IIb/III trials of osteoarthritis patients previously included in the Konstam analysis.¹²³ Although the Konstam meta-analysis cites a planned duration of follow-up of 86 weeks for these trials, the Reicen meta-analysis reports that the mean duration of

treatment was actually 3½ months. Like the Konstam study, insufficient information was provided to judge the quality of the studies analyzed or the effects of concomitant aspirin. The incidence of thrombotic cardiovascular adverse events was lower in the rofecoxib treatment group (1.93/100 patient-years) compared with the non-naproxen NSAID (ibuprofen, diclofenac, or nabumetone) groups (2.27/100 patient-years) (Table 5).

The conclusion of the Reicen analysis—that there were no significant differences between rofecoxib and non-naproxen NSAIDs—may be valid for this set of studies. However, the results do not address the more specific question of whether rofecoxib is safe at the dosage proven to reduce serious GI events associated with long-term use. The analysis combined data from all rofecoxib doses (12.5, 25, and 50 mg/day); only 545 of the patients received the 50 mg/day dose. Although 50 mg/day is higher than doses used conventionally, the issue of dose may be important because only the 50 mg dose has been shown to reduce serious GI adverse events compared to non-selective NSAIDs in a long-term trial.¹⁹ It is possible that lower doses of rofecoxib do not increase cardiovascular events compared with non-naproxen NSAIDs. However, even though lower, conventional doses of rofecoxib would be expected to be associated with lower long-term rates of GI ulcer complications compared to higher doses, this has not been proven in clinical trials.

Using a different methodology from the studies by Konstam and Reicen, a good-quality meta-analysis funded by the Swiss National Science Foundation came to different conclusions (Table 5).¹²⁴ Juni and colleagues included 18 randomized controlled trials of rofecoxib in patients with chronic musculoskeletal disorders (N=25,273), using published data on myocardial infarction as well as unpublished data available from the FDA. They found that the risk of myocardial infarction was higher in patients in the rofecoxib arms of trials compared with patients in the combined comparator arms (naproxen, non-naproxen NSAIDs, or placebo) (RR 2.24, 95% CI 1.24 to 4.02). The risk did not vary according to dose of rofecoxib or duration of therapy (shorter versus longer than 6 months). Trials with an external endpoint committee had a substantially higher risk for myocardial infarction (RR 3.88, 95% CI 1.88 to 8.02) than those without an external endpoint committee (RR 0.79, 95% CI 0.29 to 2.13). VIGOR contributed 8,076 of the 21, 432 included in the meta-analysis. However, even when the results of VIGOR were excluded, the increased risk of myocardial infarction in trials with an external endpoint committee persisted (RR 2.5, 95% CI 1.1 to 6.0).¹²⁵

Table 5. CV events in trials of rofecoxib versus non-selective NSAIDs: meta-analyses

Study	Outcome	Comparison	Relative risk (95% CI)
Konstam, 2001 ¹²²	Cardiovascular events	Rofecoxib versus non-naproxen NSAIDs	0.79 (0.40-1.55)
		Rofecoxib versus naproxen	1.69 (1.07-2.69)
Reicin, 2002 ¹²³	Cardiovascular events	Rofecoxib versus non-selective NSAIDs	1.44 (0.65-3.17)
Juni, 2004 ¹²⁴	Myocardial infarction	Rofecoxib versus any comparator	2.24 (1.24-4.02)
		Subgroup analyses:	
		Rofecoxib versus non-naproxen NSAIDs	1.55 (0.55-4.36)
		Rofecoxib versus naproxen	2.93 (1.36-6.33)

Unlike the previous meta-analyses by Reicen and Konstam, the Juni meta-analysis analyzed aggregated study-level data, evaluated the effects of variables related to methodologic quality (allocation concealment and use of an external endpoint committee), and assessed the outcome of myocardial infarction (rather than composite cardiovascular endpoints, which could have diluted the effects on myocardial infarction rates). A major point of contention, however, centers on

whether the Juni meta-analysis inappropriately combined results from different control interventions. Although Reicin and others have criticized this method of analysis because different control interventions may be associated with different risks for myocardial infarction,¹²⁶ Juni and colleagues' methods appear defensible based on their meta-regression analyses for potential sources of heterogeneity. They found that the only significant source of variation between study results was related to the use of an independent, external endpoint committee, and not to the type of control intervention. For studies with an external endpoint committee, the relative risks for myocardial infarction for rofecoxib compared with placebo, non-naproxen NSAIDs, or naproxen were 2.31, 2.98, and 3.72, respectively, with overlapping confidence intervals ($p=0.41$ for interaction).¹²⁵ The Reicin and Konstam meta-analyses did not assess the effects of this potential source of bias. Other criticisms of Juni have centered on its exclusion of two Alzheimer's trials (discussed below) and on some of its statistical methods (such as adding 0.5 to both arms of a trial when no events occurred in one of the arms). However, Juni and colleagues appeared to follow pre-specified inclusion criteria (trials of patients with musculoskeletal disease), and the statistical methods for dealing with empty cells meet current standards for conducting meta-analysis.¹²⁷ A post-hoc re-analysis of the Juni study sponsored by the manufacturer of rofecoxib and criticizing its methods and conclusions is available on-line, but has not been published in the peer-reviewed literature.¹²⁸

A fourth, fair-quality meta-analysis evaluated the cardiovascular risks of selective versus non-selective NSAIDs.¹²⁹ However, it only reported results for all COX-2 inhibitors pooled together. It is discussed in the section on cardiovascular risks associated with non-selective NSAIDs.

Rofecoxib versus placebo. The manufacturer-funded meta-analyses by Konstam and Reicin found no significant differences in cardiovascular risk between rofecoxib and placebo.^{122, 123} In the Konstam analysis, the relative risk of cardiovascular events (cardiovascular, hemorrhagic, or unknown death; nonfatal myocardial infarction; and nonfatal stroke) was 0.85 (95% CI 0.51 to 1.38).¹²² A total of 33 cardiovascular events were reported in the rofecoxib arms. In the Reicin analysis, the incidence of thrombotic cardiovascular AEs was 2.71/100 patient-years in the rofecoxib group and 2.57/100 patient-years in the placebo group (7 events reported in the rofecoxib arms).¹²³ There were too few events to evaluate the risk of myocardial infarction alone: 3 in the rofecoxib arms in one meta-analysis¹²³ and 19 fatal and nonfatal myocardial infarctions or resuscitated cardiac arrests in the other.¹²² In the Juni meta-analysis, the relative risk for myocardial infarction with rofecoxib relative to placebo was 1.04 (95% CI 0.34 to 3.12) when all trials were pooled, but 2.31 (95% CI 0.49 to 10.82) in trials with an external endpoint committee.¹²⁵

In two subsequent trials of cognitively impaired adults, rates of thrombotic vascular events were similar for rofecoxib 25 mg and placebo.^{130, 131} Four thrombotic vascular events (myocardial infarction not reported separately) occurred in 321 patients randomized to rofecoxib (1.2%) compared to 11 of 327 (3.4%) randomized to placebo in one 12-month trial of 692 patients (mean age=75.5 years) with mild to moderate Alzheimer's dementia.¹³⁰ In the second trial, 38 of 723 patients with mild cognitive impairment randomized to rofecoxib (5.2%) and 36 of 728 randomized to placebo (4.9%) had a confirmed serious thrombotic vascular event after 115-130 weeks (mean age=74.9 years); the number of confirmed nonfatal myocardial infarctions was 13 versus 10.¹³¹ However, more deaths occurred in the rofecoxib group in this trial (24 or 3.3% versus 15 or 2.1%).

On the other hand, in another long-term (the Adenomatous Polyp Prevention on Vioxx, or APPROVe) trial of a different population—that of patients receiving rofecoxib for prevention of colon polyps—rofecoxib 25 mg/day was associated with an increased risk of cardiac events (myocardial infarction, sudden death from cardiac causes, or unstable angina pectoris) relative to placebo (RR 2.80, 95% CI 1.44 to 5.45).¹³² Though the rate of events appeared to diverge only after 18 months in the initially published report,¹³² a subsequent analysis that included adverse events originally censored because they occurred more than 14 days after discontinuation of therapy suggests that the curves began to diverge by 4 to 6 months.¹³³ The risk of cerebrovascular events and peripheral vascular events were not significantly higher on rofecoxib (RR 2.32, 95% CI 0.89 to 6.74 and 0.46, 95% CI 0.08 to 2.03, respectively). Reasons for the discordant findings between the APPROVe and the Alzheimer's trials are unclear but could be related to differential underlying risk in the populations studied, duration of exposure, or differential use of aspirin or other antiplatelet agents.

The most recent and comprehensive meta-analysis included 37 placebo-controlled trials of rofecoxib.¹²⁹ It includes data from the trials evaluated in the earlier meta-analyses¹²²⁻¹²⁴ as well as newer information from the long-term polyp prevention and cognitive impairment trials. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. The meta-analysis was rated fair quality because it did not adequately assess the quality of included trials. Rofecoxib was associated with greater risks relative to placebo for the outcomes “any vascular event” (1.5% or 98/6638 versus 1.1% or 72/6415, RR 1.38, 95% CI 1.01 to 1.87) and myocardial infarction (0.8% or 54/6638 versus 0.5% or 30/6415, RR 1.76, 95% CI 1.14 to 2.73), but not for the outcomes stroke or vascular death. This is equivalent to approximately one additional myocardial infarction per 289 patients exposed to rofecoxib for one year instead of placebo. About 85% of the vascular events occurred in patients on a 25 mg dose of rofecoxib. Approximately 40% (21 of 54) of the myocardial infarctions were from the APPROVe trial.¹³²

Table 6. CV events in trials of rofecoxib versus placebo: meta-analyses

Study	Outcome	Number of events	Relative risk for (95% CI)
Konstam, 2001 ¹²²	Combined cardiovascular events	33	0.84 (0.51-1.38)
Reicin, 2002 ¹²³	Combined cardiovascular events	7	1.42 (0.24-6.22)
Juni, 2004 ¹²⁵	Myocardial infarction	Not reported	1.04 (0.34-3.12); all trials 2.31 (0.49 -10.82); only trials with external endpoint committee
Kearney, 2006 ¹²⁹	Myocardial infarction	54	1.76 (1.14-2.73)

Celecoxib. Five meta-analyses (three funded by the manufacturer of celecoxib^{62, 134, 135}) have analyzed the cardiovascular risks associated with celecoxib in primarily unpublished trials.^{62, 129, 134-136} The first, a fair-quality study by White and others, included 13 new drug application studies and two large post-marketing trials (CLASS and SUCCESS) of 18,942 patients randomized to celecoxib with osteoarthritis or rheumatoid arthritis.¹³⁴ Only two of the 15 trials were longer than 12 weeks in duration. The meta-analysis did not provide enough information about the design of the included studies to judge their quality. A total of 25 cardiovascular events (0.8%) and 6 myocardial infarctions (0.2%) occurred in patients randomized to celecoxib.

There were no differences in risk of cardiovascular events (cardiovascular, hemorrhagic and unknown deaths; nonfatal MI, or nonfatal stroke), fatal myocardial infarction, or nonfatal myocardial infarction between patients randomized to celecoxib versus those randomized to placebo, all NSAIDs, or naproxen (Table 7). There were also no differences in the subgroup of patients who were aspirin non-users. The authors did not perform an analysis of risk associated with different doses of celecoxib.

Table 7. CV events in trials of celecoxib: meta-analysis of 15 trials in patients with arthritis¹³⁴

Comparison	Relative risk for cardiovascular, hemorrhagic and unknown deaths; nonfatal MI; or nonfatal stroke (95% CI)
<i>All patients</i>	
Celecoxib versus placebo	0.85 (0.23 to 3.15)
Celecoxib versus all NSAIDs	1.06 (0.70 to 1.61)
Celecoxib versus naproxen	0.85 (0.29 to 2.46)
<i>Aspirin nonusers</i>	
Celecoxib versus placebo	0.60 (0.11 to 3.29)
Celecoxib versus all NSAIDs	0.86 (0.48 to 1.56)
Celecoxib versus naproxen	0.82 (0.18 to 3.70)

A second, more comprehensive meta-analysis was presented to the FDA's Arthritis Advisory Committee in February 2005.¹³⁵ It included 41 trials of celecoxib (N=24,933) for chronic conditions; 33 of the trials were in patients with osteoarthritis or rheumatoid arthritis. Only four of the 41 trials were longer than 12 weeks in duration. The investigators used full follow-up data from the CLASS trials (2,320 patient-years for 3,987 patients). In addition to the composite outcome of any cardiovascular thromboembolic event, the analysis also reported separate analyses for myocardial infarction, stroke, and peripheral vascular events. Over 80% of the cardiovascular events occurred in three large trials: CLASS (N=7,968), SUCCESS (N=13,194), and CAESAR (N=916) (the latter trial remains unpublished). The methods and limitations of this study were similar to the White meta-analysis. There were no significant differences between celecoxib and comparators for myocardial infarction, though event rates were low: only nine myocardial infarctions occurred among 7,462 celecoxib-exposed patients (0.12%) in the placebo-controlled trials. There were also no significant differences for any other cardiovascular thromboembolic event.

Table 8. CV events in trials of celecoxib: meta-analysis of 41 trials¹³⁵

Comparison	Relative risk for myocardial infarction (95% CI)
<i>All patients</i>	
Celecoxib \geq 200 mg/day versus placebo	1.58 (0.92-2.72)
Celecoxib \geq 200 mg/day versus non-selective NSAIDs	1.65 (0.38-7.21)
<i>Aspirin nonusers</i>	
Celecoxib \geq 200 mg/day versus placebo	1.40 (0.61-3.21)
Celecoxib \geq 200 mg/day versus non-selective NSAIDs	1.64 (0.17-15.33)

Another meta-analysis of manufacturer-held reports of 31 trials by Moore and colleagues found that celecoxib was not associated with a significantly increased risk for myocardial infarction compared with non-selective NSAIDs, any active comparator (including rofecoxib or

paracetamol), any comparator (including placebo), or any non-coxib comparator using a fixed-effect model in patients with rheumatoid or osteoarthritis, though trends towards increased risk were present (Table 9).⁶² The overall proportion of patients randomized to celecoxib with myocardial infarction was less than 0.3% (fewer than 60 cases in the largest comparison). There were too few myocardial infarctions in the celecoxib arms of trials comparing celecoxib to placebo (10 events), paracetamol (0 events), or rofecoxib (1 event) to analyze differences in risk. In the two largest trials included in the meta-analysis (CLASS and SUCCESS-I), myocardial infarctions occurred in 0.23% (29 of 12,787) of patients randomized to celecoxib 200 to 800 mg and in 0.18% (15 of 8,375) randomized to a non-selective NSAID (RR 1.7, 95% CI 0.88 to 3.2).

Although this study appears to adhere to high standards for conducting meta-analysis, its results are not verifiable because it analyzed publicly inaccessible data. In addition, myocardial infarctions in the included trials were as reported by investigators, and not subject to adjudication. The duration of exposure to celecoxib in the trials varied, with a mean of about 7 months. The authors of the meta-analysis were unable to perform an analysis on effects of duration of exposure, because the trial reports generally did not provide sufficient information on median duration of use.

Table 9. MI's in trials of celecoxib: meta-analysis of 31 trials in patients with arthritis⁶²

Comparison	Relative risk for myocardial infarction
Celecoxib 200 or 400 mg/day versus NSAID	1.9 (0.87 to 4.1)
Celecoxib any dose versus NSAID	1.6 (0.93 to 2.6)
Celecoxib any dose versus any active comparator	1.4 (0.87 to 2.3)
Celecoxib any dose versus any comparator	1.4 (0.88 to 2.2)
Celecoxib any dose versus non-coxib comparator	1.4 (0.88 to 2.2)

A fourth meta-analysis of CV risk associated with celecoxib (not funded by the manufacturer) was less comprehensive because it did not have access to all of the trial data.¹³⁶ It limited its analysis to trials that were at least 6 weeks duration and reported cardiovascular events in published articles or publicly available material on the FDA or manufacturer website, and also differed from the Moore analysis by including trials of patients receiving celecoxib for colon polyp prevention and Alzheimer's disease. It found that the risk of myocardial infarction was increased in 3 trials (APC, ADAPT, PreSAP; none of arthritis patients) comparing celecoxib to placebo (OR 2.26, 95% CI 1.0 to 5.1) and in 5 trials (APC, CLASS, ADAPT, PreSAP, VACT; the latter 2 of arthritis patients) comparing celecoxib to placebo, diclofenac, ibuprofen, or paracetamol (OR 1.88, 95% CI 1.15 to 3.08) (Table 10). No heterogeneity was present. There was no association between celecoxib use and either cerebrovascular events, cardiovascular death, or composite cardiovascular events. Although this study was rated good quality, lack of comprehensiveness is a concern because it excluded 42 celecoxib trials either because they were shorter than 6 weeks or because publicly available information on cardiovascular events was not available. In addition, nearly two-thirds (18 of 29) of the myocardial infarctions in the placebo-controlled trials (the primary analysis) came from the APC (polyp prevention) trial. On the other hand, the meta-analysis also did not include the recently published, large (N=13,274), 12-week SUCCESS-I Study, which reported results consistent with its findings (10 myocardial infarctions or 0.55/100 patient-years in the combined celecoxib arms versus 1 myocardial infarction or 0.11/100 patient-years in the combined non-selective NSAID arms).⁶³

Table 10. MI's in trials of celecoxib: meta-analysis of trials of at least 6 weeks duration with published or publicly available data¹³⁶

Comparison	Relative risk for myocardial infarction
Celecoxib any dose versus placebo (3 trials)	2.3 (1.0 to 5.1)
Celecoxib any dose versus placebo, diclofenac, ibuprofen, or paracetamol	1.9 (1.2 to 3.1)

The fifth meta-analysis (also not funded by the manufacturer) analyzed data from 41 published and unpublished trials of celecoxib (8,976 patient-years of exposure).¹²⁹ Nine of the trials were longer than 12 weeks in duration. Characteristics of this study, which also evaluated cardiovascular risks associated with other selective and non-selective NSAIDs, are discussed in the rofecoxib section above. Data on celecoxib risk primarily came from patients with osteoarthritis or rheumatoid arthritis (33 trials), but studies of low back or temporomandibular joint pain, ankylosing spondylitis, Alzheimer's disease, and colon polyp prevention were also included. Myocardial infarction rates were higher with celecoxib relative to placebo (0.5% or 44/8976 person-years versus 0.2% or 9/4953, RR 2.13, 95% CI 1.20 to 3.80), and for combined vascular events (0.9% vs. 0.6%, RR 1.51, 95% CI 1.02 to 2.24), but there were no significant differences in risk of stroke alone or vascular death (Table 11). This is equivalent to approximately one additional myocardial infarction for every 325 patients treated with celecoxib instead of placebo for one year. The 99% confidence interval (reported in the article because of multiple subgroup analyses) remained significant for myocardial infarction, but not for combined vascular events. Two large polyp prevention trials accounted for about 60% (27 of 44) of the myocardial infarctions in patients randomized to celecoxib.¹⁰⁹ A trend towards increased risk of vascular events ($p=0.03$) with higher doses of celecoxib was present, but nearly all of the events at the highest (800 mg daily) dose occurred in the polyp prevention trials. Analyses on the effects of duration and independent event adjudication were not stratified by specific COX-2 inhibitor, nor were estimates of cardiovascular risk with specific COX-2 inhibitors relative to naproxen or non-naproxen NSAIDs (see section on CV risk of non-selective NSAIDs).

Table 11. CV events in trials of celecoxib: meta-analysis of 41 trials of at least 4 weeks duration¹²⁹

Comparison	Outcome	Relative risk (95% CI)
Celecoxib any dose versus placebo	Any vascular event	1.5 (1.0 to 2.2)
Celecoxib any dose versus placebo	Myocardial infarction	2.1 (1.2 to 3.8)
Celecoxib any dose versus placebo	Stroke	1.1 (0.6 to 2.2)
Celecoxib any dose versus placebo	Vascular death	1.3 (0.6 to 2.8)

The estimates of risk for myocardial infarction with celecoxib relative to placebo in the non-manufacturer-funded meta-analyses^{129, 136} are higher than in the manufacturer-funded meta-analyses.^{134, 135} The major reason for the difference in estimates appears to be the inclusion of two recent, long-term trials of colon polyp prevention (APC and PreSAP) in the former.^{108, 110} A large number of myocardial infarctions occurred in these trials (27, compared to a total of nine in the most comprehensive manufacturer-funded meta-analysis¹³⁵), and estimates of risk from both trials were higher than previous pooled estimates without these trials (RR 1.58, 95% CI 0.92 to 2.72).¹³⁵ In one meta-analysis,^{129, 136} the rate of nonfatal myocardial infarction was 1.3% (18/1356) with celecoxib (200 or 400 mg twice daily) versus 0.4% (3/679) with placebo (RR

2.67, 95% CI 0.5 to 8.41) in the APC trial¹⁰⁸ and 1.0% (9/933) versus 0.5% (3/628) for a relative risk of 1.84 (95% CI 0.54 to 6.28) in PreSAP (400 mg once daily).¹¹⁰ A subsequent analysis of the APC trial and PreSAP using slightly different data (due to the identification of additional events after study closure) reported a pooled relative risk of 1.9 (95% CI 1.1 to 3.1, no heterogeneity) for the composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure.¹⁰⁹ Rates of fatal or nonfatal myocardial infarction in were 1.6% (22/1356) versus 0.4% (3/679) in the APC trial and 9/933 (1.0%) vs. 4/628 (0.6%) in PreSAP.

In summary, celecoxib appears associated with an increased risk of myocardial infarctions or thromboembolic cardiovascular events relative to placebo. Much of the evidence for increased cardiovascular risk comes from two large, long-term polyp prevention studies comparing celecoxib 200 or 400 mg twice daily, or 400 mg once daily to placebo. Although trends toward increased myocardial infarction risk with celecoxib relative to placebo as well as relative to other NSAIDs are also present in meta-analyses of primarily short-term trials of arthritis patients, small numbers of events limit the precision of estimates from those trials.

Observational Studies of GI and CV Safety

Overview. Numerous long-term observational studies have evaluated the GI and CV risks associated with selective and non-selective NSAIDs. The studies primarily relied on claims data or other administrative databases or on electronic medical record data collected in practice networks to identify cases, and prescription claims to determine exposure. A strength of these studies is that they evaluated much larger populations than could be enrolled into clinical trials.¹³⁷ In addition, they reflect how coxibs and other NSAIDs are actually used in practice better than many clinical trials, which are usually short term, require rigid dosing regimens, limit the use of other drugs, and implement strategies to monitor and enhance compliance. Population- and practice-based studies may also better represent patients who would be excluded from randomized trials because of comorbidities, age, or other factors.

On the other hand, the most important weakness of observational studies is that patients are allocated treatment in a non-randomized manner. This can lead to biased estimates of effects even when appropriate statistical adjustment on a variety of confounding variables is performed.⁴⁰ In addition, data sources typically cannot reliably assess over-the-counter aspirin, NSAIDs, or acid-suppressing medication use,¹³⁷ and information on prescription fills may not always accurately correspond to the actual degree of exposure to the drugs.

Rofecoxib. Five observational studies reported rates of serious GI events for rofecoxib relative to celecoxib, NSAIDs, and non-use.¹³⁸⁻¹⁴² (Table 12). In direct comparisons, rofecoxib was associated with a similar risk of upper GI complications compared to meloxicam,¹⁴⁰ but a greater risk of upper GI hemorrhage than celecoxib, non-selective NSAIDs, and diclofenac plus misoprostol.^{139, 142} In a nested case-control study, the risk of upper GI bleeding was modestly higher for rofecoxib compared to celecoxib, NSAIDs, or non-use (RR in the range of 1 to 2).¹³⁸ Another case-control study that reported higher relative risks of serious GI events with rofecoxib should be interpreted with caution because exposure information was ascertained using unblinded patient interviewing, which is more susceptible to recall bias than blinded coding of exposures status from prescription or general practice databases.¹⁴¹

Analyses of the effects of exposure duration, dosage, and study duration on risk of serious GI events were generally not reported. In fact, COX-2 dosages were only reported in one study

which reported that the proportion of patients on celecoxib receiving >200 mg/day was 19%, and the proportion of patients on rofecoxib on >25 mg/day was 8%.¹³⁹

Table 12. Serious GI events in observational studies

Author, Year Study design Sample size	Mean age (yrs)	Duration (days)	Outcome	Main findings
Hippisley-Cox 2005 ¹³⁸ Case-control Cases: 9407	NR; ≥ 25	Unclear	Complicated GI event	↑ <i>risk relative to non-use</i> : No for celecoxib (RR 1.25; 95% CI 0.91, 1.72) Yes for rofecoxib (RR 1.79; 95% CI 1.42, 2.26); overall selective (RR 1.72; 95% CI 1.29, 2.29) and non-selective NSAIDs (1.67; 95% CI 1.43, 1.94); ibuprofen (RR 1.58; 95% CI 1.37, 1.83); diclofenac (RR 2.07; 95% CI 1.82, 2.35); naproxen (RR 1.97; 95% CI 1.48, 2.61)
Mamdani 2002 ¹³⁹ Cohort n=143,969	75.7	141	Upper GI hemorrhage	↑ <i>risk relative to celecoxib</i> : Yes for rofecoxib (RR 1.9; 95% CI 1.2, 2.8), non-selective NSAIDs (RR 1.9; 95% CI 1.0, 3.5) and diclofenac+ misoprostol (RR 3.2; 95% CI 1.6, 6.5)
Layton 2003 ¹⁴⁰ Cohort n=34,355	60.4-62.5	270	Upper GI complications (perforations/bleeding)	Similar risk for rofecoxib and meloxicam (RR 0.91; 95% CI 0.59, 1.42)
Laporte 2004 ¹⁴¹ Case-control Cases=2,813	NR; ≥ 18	NR	Upper GI bleeding	↑ <i>risk vs. non-use</i> for rofecoxib (RR 7.2; 95% CI 2.3, 23.0), diclofenac (RR 3.7; 95% CI 2.6, 5.4), ibuprofen (RR 3.1; 95% CI 2.0, 4.9), indomethacin (RR 10.0; 95% CI 4.4, 22.6), ketoprofen (RR 10.0; 95% CI 3.9, 25.8), ketorolac (RR 24.7; 95% CI 8.0, 77.0), meloxicam (RR 5.7; 95% CI 2.2, 15.0), naproxen (RR 10.0; 95% CI 5.7, 17.6), nimesulide (RR 3.2; 95% CI 1.9, 5.6), piroxicam (RR 15.5; 95% CI 10.0, 24.2)
Kasliwal 2006 ¹⁴² Cohort n=32,726	62.5	Median Rofecoxib=111 Celecoxib=90 p<0.0001	Upper GI complications (perforations/bleeding)	Rofecoxib versus celecoxib aRR (95% CI): 1.60 (0.95, 2.70)

Fourteen observational studies evaluated the risk of cardiovascular events associated with rofecoxib (Table 13).¹⁴²⁻¹⁵⁵ Interpretation of the studies is complicated by the use of different study designs, adjustment for different confounders, and evaluation of different populations and outcomes. Six of these studies appeared to rely exclusively on administrative and pharmaceutical databases to determine outcomes, exposures, and comorbidities.^{143, 147, 149-152} The other studies supplemented administrative or claims data with chart review,^{145, 153} clinical or practice-based databases,^{146, 148, 155} or telephone interviews.¹⁴⁴ An interim analysis of one study relied on a combination of a medication surveillance database, physician questionnaires, hospital admission data, spontaneous reports, and national morbidity and mortality databases.¹⁵⁴

Several studies indicate that using claims data is quite accurate (positive predictive value >90%) for identifying myocardial infarction.^{156, 157} A weakness of relying exclusively on administrative databases, however, is that they frequently have incomplete information about potentially important confounders such as income level, obesity, smoking status, and level of

education.¹⁵⁷ All three of the observational studies that collected information about body mass index, for example, supplemented administrative databases with other sources.¹⁴⁴⁻¹⁴⁶

Unmeasured confounders could result in less accurate estimates of cardiovascular risk, though one analysis suggests that the effects would be only modest.¹⁵⁸ On the other hand, studies can also ‘overcontrol’ if they attempt to adjust for cardiovascular risk factors identified after the initiation of treatment, when the risk factors are actually intermediate effects of the drugs themselves that predispose to subsequent cardiovascular events.¹⁵⁹

Rofecoxib was associated with an increased risk of CV events relative to non-selective NSAIDs in three of five studies^{40, 144, 152, 153} and an increased risk relative to celecoxib in three of five studies.^{142, 144, 145, 154, 160} In studies that compared rofecoxib, celecoxib, or NSAID use to non-use, none of the drugs were consistently associated with increased risk of CV events.^{143, 146, 147, 149, 151, 155} CV event risk estimates from two observational studies of rofecoxib relative to naproxen (Solomon 2004¹⁴⁵: OR 1.17, 95% CI 0.90, 1.52; Kimmel 2005¹⁴⁴: OR 3.30, 95% CI 1.37, 8.40) were lower than the estimated relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen in VIGOR.¹⁰³ It is likely that the inconsistencies in effect magnitudes were due in large part to population differences and study methodology. For example, risk estimates from the Solomon 2004 study¹⁴⁵ may only be generalizable to a population that is of a more advanced age than that of VIGOR (81.6 vs. 58 years) and of a possibly lower income level, as it focused on low-income Medicare beneficiaries. Participants in the Kimmel 2005 study,¹⁴⁴ on the other hand, were similar in mean age to those in VIGOR (53.1 vs. 58 years), but different methods of data ascertainment may have affected risk estimates. This study, which found the highest risk of MI associated with rofecoxib compared with celecoxib (OR 2.72), differed from the others in that it collected information about exposures and covariates using structured telephone interviews rather than by using administrative or large practice databases.¹⁴⁴ The use of structured telephone interviews could have enhanced the ability of the investigators to measure relevant confounders and drug exposures. On the other hand, participation bias (only 50% of those approached participated) and recall bias could have skewed the results, though it is not clear that such biases should favor either rofecoxib or celecoxib.

Results of studies that found similar risk of CV events with rofecoxib and meloxicam¹⁵² or celecoxib^{142, 154} may also be less reliable. These studies adjusted for far fewer demographic and prognostic factors than other studies that adjusted for multiple demographic factors and comorbidities.

Another factor that varied between studies was how exposure status was defined. In one of the studies that reported no association between rofecoxib use and cardiovascular thrombotic events, use of selective COX-2 inhibitors was defined as prescriptions within 6 months of the index date.¹⁵⁰ By contrast, other studies defined current use as occurring on or near the index date, which strengthens confidence in inferences about the link between rofecoxib and the observed MIs.

Table 13. Cardiovascular events in observational studies

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Levesque 2005 ¹⁴³ Cohort n=59724	NR; ≥ 66	22.50%	844.8	Acute MI, fatal or nonfatal ↑ risk relative to NSAID non-use: Yes for rofecoxib, regardless of dose (Overall RR 1.24; 95% CI 1.05, 1.46) No for celecoxib (Overall RR 0.99; 95% CI 0.85, 1.16), naproxen (RR 1.17; 95% CI 0.75, 1.84) or meloxicam (95% CI 1.06; 95% CI 0.49, 2.30)
Kimmel 2005 ¹⁴⁴ Case-control Cases: 1718	NR; aged 40 to 75	33.60%	NR	Nonfatal MI ↑ risk for rofecoxib when directly compared with celecoxib (OR 2.72; 95% CI 1.24 to 5.95) or naproxen (OR 3.39; 95% CI 1.37, 8.40) ↑ risk for rofecoxib* relative to ibuprofen or diclofenac (OR 2.04; 95% CI 1.16, 3.60) or naproxen (OR 3.30; 95% CI 1.37, 8.40) Risk for celecoxib* similar to ibuprofen or diclofenac (OR 0.77; 95% CI 0.4, 1.48) or naproxen (OR 0.81; 95% CI 0.37, 1.77) *Regardless of aspirin use
Solomon 2004 ¹⁴⁵ Case-control Cases=10,895	NR; > 80	NR	1-30 days 31-90 days > 90 days	Acute MI ↑ risk for rofecoxib relative to celecoxib (OR 1.24; 95% CI 1.05, 1.46) Risk for rofecoxib similar to naproxen (aOR 1.17; 95% CI 0.9, 1.52) or ibuprofen (aOR 1.21; 95% CI 0.92, 1.58) or other NSAIDs (aOR 1.17; 95% CI 0.99, 1.38) Risk for celecoxib similar to naproxen (aOR 0.95; 95% CI 0.74, 1.21) or ibuprofen (aOR 0.98; 95% CI 0.76, 1.26) or other NSAIDs (aOR 0.95, 95% CI 0.82, 1.10)
Hippisley-Cox 2005 ¹⁴⁶ Case-control Cases: 9218	NR; aged 25-100	NR	NR	First ever MI ↑ risk relative to nonuse: Yes for rofecoxib (aOR 1.32; 95% CI 1.09, 1.61), other selective NSAIDs (aOR 1.27; 95% CI 1.00, 1.61), ibuprofen (aOR 1.24; 95% CI 1.11, 1.39), diclofenac (aOR 1.55; 95% CI 1.39, 1.72), naproxen (aOR 1.27; 95% CI 1.01, 1.60) and other non-selective NSAIDs (aOR 1.21; 95% CI 1.02, 1.44) No for celecoxib (aOR 1.21; 95% CI 0.96, 1.54)
Mamdani 2003 ¹⁴⁷ Cohort n=166,964	NR; ≥ 66	14.70%	165.6	Incidence of hospitalization for acute MI: risk relative to non-use Similar risk for rofecoxib (aRR 1.0; 95% CI 0.8, 1.4), celecoxib (aRR 0.9; 95% CI 0.7, 1.4), naproxen (aRR 1.0; 95% CI 0.6, 1.7), or non-naproxen non-selective NSAIDs (aRR 1.2; 95% CI 0.9, 1.4)
Graham 2005 ¹⁶⁰ Case-control Cases=8,143	NR: 18-84	Telephone interview subgroup (n=817): 23%	Mean=113 days before event	Acute MI requiring admission or sudden cardiac death: risk relative to celecoxib ↑ risk for rofecoxib for all dosages (aOR 1.59; 95% CI 1.10, 2.32) or for dosages > 25 mg (aOR 3.58; 95% CI 1.27, 10.11), but dosages ≤ 25 mg had risk similar to celecoxib (aOR 1.47; 95% CI 0.99, 2.17) ↑ risk for ibuprofen (aOR 1.26; 95% CI 1.00, 1.60), naproxen (aOR 1.36; 95% CI 1.06, 1.75), or other NSAIDs (aOR 1.35; 95% CI 1.06, 1.72)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Johnsen 2005 ¹⁴⁹ Case-control Cases=10,280	69.6	6.9% high dose	NR	Acute MI: risk relative to nonusers ↑ risk current (aRR 1.80; 95% CI 1.47, 2.21) and new users (aRR 2.52; 95% CI 1.45, 3.13) of rofecoxib ↑ risk for new users of celecoxib (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62) Similar risk for new (aRR 1.65; 95% CI 0.57, 4.83) or current users of naproxen (aRR 1.50; 95% CI 0.99, 2.29) relative to nonuse ↑ risk for new (aRR 2.65; 95% CI 2.00, 3.50) or current users of other nonaspirin NSAIDs (aRR 1.68; 95% CI 1.52, 1.85) naproxen (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62)
Shaya 2005 ¹⁵⁰ Cohort n=6,250 50% black	NR; 70% were aged 50 years or younger	NR	≥ 60 prior to event	Cardiovascular thrombotic events: relative to non-naproxen NSAIDs Similar for rofecoxib (aOR 0.99; 95% CI 0.76, 1.30) or celecoxib (aOR 1.19; 95% CI 0.93, 1.51)
Ray 2002 ¹⁶¹ Cohort n=378,776	61.5	NR	NR	Serious CHD (hospital admission for AMI or death from CHD): relative to non-use Similar risks for rofecoxib at dosages ≤ 25 mg (aRR 1.03; 95% CI 0.78, 1.35) or > 25 mg (aRR 1.70; 95% CI 0.98, 2.95), celecoxib (aRR 0.96; 95% CI 0.76, 1.21), ibuprofen (aRR 0.91; 95% CI 0.78, 1.06), or naproxen (aRR 0.93; 95% CI 0.82, 1.06) relative to nonuse
Layton 2003 ¹⁵² Cohort n=34,355	NR	NR	270	Thromboembolic events: Rofecoxib vs meloxicam (A) cardiovascular: similar risk (RR 1.38; 95% CI 0.71, 2.67) (B) cerebrovascular: increased risk with rofecoxib (RR 1.68; 95% CI 1.15, 2.46) (C) peripheral venous thrombotic: lower risk for rofecoxib (RR 0.29; 95% CI 0.11, 0.78)
Velentgas 2005 ¹⁵³ Cohort n=424,584	NR (40-64 years)	NR	5.1 months	Combined endpoint of acute coronary syndrome and myocardial infarction: risk relative to ibuprofen or diclofenac (adjusted rate ratios) Increased risk for current use of rofecoxib (1.35; 95% CI 1.09, 1.68) and but not for recent use (1.15; 95% CI 0.88, 1.50) No increased risk for current (1.03; 95% CI 0.83, 1.27) or recent use of celecoxib (0.91; 95% CI 0.70, 1.17) No increased risk for current (1.14 95% CI 0.93, 1.39) or recent use of naproxen (0.86; 95% CI 0.70, 1.04)
Harrison-Woolrych 2005 ¹⁵⁴ Cohort Interim analysis of 11,149 of 58,849 who completed follow-up by 11/30/04	NR	NR	NR	Thrombotic cardiovascular events Celecoxib and rofecoxib were associated with similar risks (aHR 0.94; 95% CI 0.51, 1.70)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Andersohn 2006 ¹⁵⁵ Case-control Cases=3,643	68.7	NR	Mean=542 days	aRR (95% CI) for diagnosis of AMI, death from AMI, or sudden death from coronary heart disease (CHD) relative to nonuse: Increased risk for celecoxib 1.56 (1.23, 1.98), rofecoxib 1.33 (1.06, 1.67), etoricoxib 2.02 (1.08, 3.80) and diclofenac 1.36 (1.17, 1.58) No increased risk for valdecoxib 4.26 (0.60, 30.27), ibuprofen 1.00 (0.83, 1.21) or naproxen 1.16 (0.86, 1.58)
Kasliwal 2006 ¹⁴² Cohort n=32,726	62.5	Rofecoxib=35.3% Celecoxib=21.9% P<0.0001	Median Rofecoxib=111 Celecoxib=90 p<0.0001	aRR (95% CI) for rofecoxib versus celecoxib (adjusted for age, age ² , sex, and concomitant use of the combination of aspirin and/or antiplatelet/anticoagulant agents (a) Cardiovascular TE: 1.04 (0.50, 2.17) (b) Cerebrovascular TE: 1.43 (0.86, 2.38) (c) Peripheral venous (DVT/PE): 0.36 (0.01, 1.34)

aOR=adjusted odds ratio; aRR=adjusted relative risk; aIRR=adjusted incidence rate ratios; aHR=adjusted hazard ratio;
CI=confidence interval

Celecoxib. As summarized above, celecoxib was consistently associated with lower risks of serious GI¹³⁹ and CV events^{144, 145, 160} than rofecoxib in several observational studies. Observational studies also demonstrated that, compared with non-selective NSAIDs, celecoxib was consistently GI protective^{139, 162} or neutral¹³⁸ and was never associated with higher risks of CV events.^{144, 145, 150, 160}

Specifically, with regard to GI safety, celecoxib was associated with significantly lower risks of GI hemorrhage when directly compared to non-selective NSAIDs (relative risk 0.23, 95% CI 0.12, 0.43)¹³⁹ and of perforation or bleeding compared to meloxicam (RR 0.56; 95% CI 0.32, 0.96).¹⁶² Risk of complicated GI events was significantly lower for NSAID nonuse relative to numerous NSAIDs (i.e., selective NSAIDs, ibuprofen, diclofenac, naproxen, non-selective) but was similar relative to celecoxib.¹³⁸

With regard to CV safety, celecoxib was associated with similar risks (estimate range 0.77 to 1.19) of serious CV events compared to ibuprofen, diclofenac, naproxen, and “other NSAIDs”^{144, 145, 150} and, in one study, was associated with significantly lower risks of acute MI requiring admission or sudden cardiac death than ibuprofen, naproxen, or other NSAIDs.¹⁶⁰

Relative to non-use, some observational studies have shown an increased risk of MI associated with celecoxib^{149, 155}, whereas others have not.^{143, 146, 147} In the two studies that found an association, the increased MI risk was either time-dependent¹⁴⁹ or dose-dependent.¹⁵⁵

Additional analysis of observational studies. An important limitation of the observational studies is that they did not simultaneously assess the risk for serious cardiac and GI events. We re-analyzed data from three studies that reported rates of acute myocardial infarction,¹⁴⁷ hospital admissions for congestive heart failure,¹⁶³ and upper gastrointestinal bleeding¹³⁹ in a large cohort of elderly patients in Ontario, Canada, to estimate the net effects of selective and non-selective NSAIDs on serious cardiovascular and GI events in this population. Although the three studies evaluated the cohort at slightly different points in time, study methods and populations characteristics appeared essentially identical.

We calculated the effects of selective and non-selective NSAIDs on numbers of acute myocardial infarction, upper GI bleed, and hospitalization for heart failure using baseline rates of events in patients not exposed to NSAIDs and estimates of risk as reported in the studies (Table 14). We then estimated the net effects on all three serious adverse events using Monte Carlo simulation (see Methods section for additional details).

Table 14. Baseline rates of MI, upper GI bleed, and congestive heart failure (CHF) and risk associated with selective and non-selective NSAIDs in an Ontario cohort of elderly persons

Adverse event	Study, year	Baseline rates (per 1000 person-years)	Risk with celecoxib	Risk with rofecoxib	Risk with non-selective NSAIDs	Risk with naproxen
Myocardial infarction	Mamdani, 2003 ¹⁴⁷	8.2	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.4)	1.5 (1.2 to 1.8)	1.0 (0.6 to 1.7)
Upper GI bleed	Mamdani, 2002 ¹³⁹	2.2	1.0 (0.7 to 1.6)	1.9 (1.3 to 2.8)	4.0 (2.3 to 6.9)	4.0 (2.3 to 6.9)
Heart failure admission	Mamdani, 2004 ¹⁶³	9.1	1.0 (0.8 to 1.3)	1.8 (1.5 to 2.2)	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.9)

Our results (see Table 15) suggest that in this population, under real-world conditions, use of celecoxib was neutral with regard to these adverse events when compared with non-use. On the other hand, use of rofecoxib, non-selective NSAIDs, and naproxen were all associated with more serious adverse events than they prevented (Table 15). Rofecoxib and naproxen essentially appeared equivalent when considering all three adverse events together, though rofecoxib was associated with more heart failure admissions and fewer GI bleeds. Our estimates are consistent with analyses of serious adverse events in VIGOR (discussed earlier), which found that rates were essentially equivalent for rofecoxib and non-selective NSAIDs.^{113, 114} However, the result are discordant from analyses of serious adverse events in CLASS, which found that celecoxib offered no advantage over non-selective NSAIDs.^{94, 113} Differences in populations (the Ontario cohort only enrolled patients over 65 years old who filled multiple prescriptions), indications for starting celecoxib, dosing of celecoxib, or co-medication use might account for this discrepancy. In addition, because these studies only included patients who filled multiple prescriptions for NSAIDs, the analyses could underestimate early adverse events.

Table 15. Effects of selective or non-selective NSAIDs on number of serious adverse events

	Estimated effect on MI's (number per 1000 person-years)	Estimated effect on GI bleed (number per 1000 person-years)	Estimated effect on heart failure admissions (number per 1000 person-years)	Net effect on number of MI's, GI bleeds, and heart failure admissions (number per 1000 person-years)
Celecoxib	-0.82 (-2.46 to 1.64)	0 (-0.66 to 1.32)	0 (-1.82 to 2.73)	-0.70 (-3.58 to 2.71)
Rofecoxib	0 (-1.64 to 3.28)	+1.98 (0.66 to 3.96)	+7.28 (4.55 to 10.92)	+9.42 (5.47 to 13.99)
Non-selective NSAIDs	+4.1 (1.64 to 6.56)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+14.68 (8.59 to 22.72)
Naproxen	0 (-3.28 to 5.74)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+10.77 (3.92 to 19.89)

GI and CV Safety of Valdecoxib

The risk of clinically significant upper GI events (bleeding, perforation, and gastric outlet obstruction) with valdecoxib was evaluated in a fair-quality, manufacturer-funded meta-analysis of eight randomized controlled trials of 12 to 26 weeks duration.¹¹⁷ This study prospectively defined ulcer complications and used independent adjudication to determine adverse events. However, it is not described how assiduously the trials adhered to the adjudication process. Four of the trials were not published, and there was insufficient information about study design to determine the quality of the trials. The meta-analysis found valdecoxib associated with a significantly lower rate of significant upper GI events compared with non-selective NSAIDs (0.68% vs. 1.96%, all patients; 0.29% vs. 2.08%, non-aspirin users; $p < 0.05$). Another meta-analysis of five trials by the same authors found valdecoxib associated with a lower risk of 'moderate-to-severe' upper GI symptoms compared with non-specific NSAIDs (HR 0.59, 95% CI 0.47 to 0.74) and similar risk relative to placebo.¹⁶⁴ Adverse events were self-reported by patients in these trials, and the quality of the trials was not assessed by the meta-analysts. Two of the included trials were published only in abstract form.

We found no published trials evaluating the risk of cardiovascular events associated with valdecoxib in patients with arthritis. Valdecoxib was not associated with an increased risk of cardiovascular events relative to placebo or other NSAIDs in any of three fair-quality meta-analyses of primarily unpublished data. The ability to detect increased cardiovascular risk in all of these meta-analyses is limited by small numbers of events. A meta-analysis funded by Pfizer and presented to the FDA in February 2005 analyzed primarily unpublished data from 19 trials of patients with chronic pain (methods described above in the section on celecoxib).¹³⁵ Thirteen studies were of patients with osteoarthritis or rheumatoid arthritis. Three were longer than 12 weeks in duration. There was no association between valdecoxib use and either cardiovascular thromboembolic events or myocardial infarction (Table 16). However, only 5 of 4,438 patients (0.2%) randomized to valdecoxib in the placebo-controlled trials and 6 of 4,591 (0.1%) in the active-controlled trials had a cardiovascular event. An earlier meta-analysis of 10 trials (also funded by Pfizer, and using similar methods) also found no difference in risk for myocardial infarction between valdecoxib and either placebo or other NSAIDs.¹³⁴

Table 16. Myocardial infarction in trials of valdecoxib for chronic pain: meta-analysis of 19 trials¹³⁵

Comparison	Relative risk for myocardial infarction
Valdecoxib ≥ 10 mg/day versus placebo	1.80 (0.47-6.97)
Valdecoxib ≥ 10 mg/day versus non-selective NSAID	0.32 (0.12-0.87)

The most recent meta-analysis (not funded by the manufacturer) included 14 placebo-controlled trials (Table 17).¹²⁹ There were no significant differences between valdecoxib and placebo for the outcomes any vascular event (RR 1.47, 95% CI 0.44 to 4.95), myocardial infarction (RR 1.65, 95% CI 0.28 to 9.87), stroke (RR 0.85, 95% CI 0.07 to 10.6) or vascular death (RR 2.72, 95% CI 0.49 to 15.2). A total of 14 vascular events (1.9%) and 8 myocardial infarctions (1.1%) occurred among the 748 patients in the valdecoxib arms.

Table 17. Cardiovascular events in trials of valdecoxib versus placebo: meta-analysis of 14 trials¹²⁹

Comparison	Outcome	Relative risk
Valdecoxib versus placebo	Any vascular event	1.47 (0.44-4.95)
Valdecoxib versus placebo	Myocardial infarction	1.65 (0.28-9.87)
Valdecoxib versus placebo	Stroke	0.85 (0.07-10.6)
Valdecoxib versus placebo	Vascular death	2.72 (0.49-15.2)

None of the meta-analyses included two short-term (<2 month) trials in the high-risk setting of post-coronary artery bypass surgery.^{165, 166} In these trials, parecoxib (an intravenous coxib rapidly converted to valdecoxib) followed by valdecoxib (40 mg bid¹⁶⁵ or 20 mg bid¹⁶⁶) was associated with a two- to three-fold higher short-term risk of cardiovascular events compared with placebo (pooled relative risk 3.08, 95% CI 1.20 to 7.87).¹⁶⁷

FDA information. A warning was added to the valdecoxib product label in November, 2002. It was prompted by reports of cases of serious anaphylactic reactions and serious dermatologic adverse events in postmarketing surveillance.¹⁶⁸ A study of two large European data sources and the US FDA spontaneous adverse events reporting system prior to the introduction of COX-2 inhibitors found other NSAIDs—in particular piroxicam and tenoxicam—also associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.¹⁶⁹ However, the rates of these events were extremely low, on the order of one per 100,000 or less during an initial 8-week course of therapy.

GI and CV Safety of Etoricoxib

A fair quality meta-analysis of ten RCTs, which included long-term (>1 year) data from 7 trials of OA, RA, or ankylosing spondylitis patients, found etoricoxib at doses ranging from 5 to 120 mg/day (mean dose 87 mg/day) associated with a lower risk of confirmed PUBs (upper GI perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding) compared to diclofenac 150 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day (1.24% vs. 2.48%, RR 0.48, 95% CI 0.32, 0.73).¹⁷⁰ This meta-analysis was rated fair quality because it did not provide adequate detail of the included trials and did not evaluate the effects of dose, duration, or other potential sources of heterogeneity. In addition, it included results of noncomparative extension phases in its analyses, resulting in unequal durations of follow-up for the etoricoxib group (median 12.4 months) compared to the non-selective NSAID groups (median 6.3 months). There were too few events in patients on concomitant aspirin (8 overall) to evaluate its effects on GI safety. An earlier meta-analysis that used similar methods to analyze rates of perforations, symptomatic ulcers, and bleeds reported similar results.¹⁷¹

There is only limited evidence regarding the CV risk associated with long-term use of etoricoxib. One 52-week trial reported that no patients randomized to naproxen and five (2%) randomized to etoricoxib (four receiving 90 mg/day; one 120 mg/day) experienced a serious cardiovascular adverse event.¹⁷²

Three meta-analyses have evaluated cardiovascular risks associated with etoricoxib. The largest and most recent meta-analysis (by Kearney and colleagues) included 17 placebo-controlled trials of patients (1,167 person-years of exposure) mainly with osteoarthritis or rheumatoid arthritis.¹²⁹ Most of the trials had short (less than 12 weeks) placebo-controlled periods. There was no difference between etoricoxib and placebo for risk of any vascular event (RR 1.78, 95% CI 0.43 to 7.40), myocardial infarction (RR 4.48, 95% CI 0.20 to 99.4), stroke

(RR 1.17, 95% CI 0.21 to 6.51), or vascular death (RR 4.48, 95% CI 0.36 to 56.3). The number of cardiovascular events was very low, with only two myocardial infarctions over 753 person-years of exposure to etoricoxib (0.3%). A less-comprehensive systematic review of five short-term trials (all included in the Kearney meta-analysis) also found no significant increased risk of thromboembolic event (pulmonary embolism, deep vein thrombosis, myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack) with etoricoxib (dose range 30 to 90 mg) versus placebo (OR 1.49, 95% CI 0.42-5.31).¹⁷³ A third meta-analysis (available only as an abstract) of 12 trials of unspecified durations found that the cardiovascular safety of etoricoxib compared favorably to placebo and non-selective NSAIDs (RR 1.11, 95% CI 0.32, 3.81 and RR 0.83, 95% CI 0.26, 2.64, respectively) though there was a trend towards increased risk compared to naproxen (RR 1.70, 95% CI 0.91, 3.18).¹⁷⁴

GI and CV Safety of Lumiracoxib

One large (N=18,325), long-term (52 weeks) study of osteoarthritis patients (The Therapeutic Arthritis Research and Gastrointestinal Event Trial, or TARGET) compared the safety of a supratherapeutic dose of lumiracoxib (400 mg/day) to naproxen (1000 mg/day) or ibuprofen (2400 mg/day) over 52 weeks.¹⁷⁵⁻¹⁷⁷ In patients not taking aspirin, lumiracoxib was associated with a lower risk of bleeding, perforation, or obstruction compared to naproxen or ibuprofen (HR 0.21, 95% CI 0.12, 0.37, 1-year incidence of ulcer complications 0.25% vs. 1.09%).¹⁷⁵ There was no difference in ulcer complication risk among aspirin users (HR 0.79, 95% CI 0.40, 1.55). The rate of myocardial infarction was low, ranging from 0.16% to 0.38%, and there were no statistically significant differences between interventions (HR 1.77 for lumiracoxib versus naproxen, 95% CI 0.82, 3.84 and HR 0.66 for lumiracoxib versus ibuprofen, 95% CI 0.21, 2.09).¹⁷⁷

A recent fair-quality meta-analysis of 12 primarily short-term trials found no significant increase in risk of vascular events (RR 1.13, 95% CI 0.43 to 2.93), myocardial infarction (RR 1.07, 95% CI 0.20 to 5.63), stroke (RR 0.63, 95% CI 0.13 to 3.11), or vascular death (RR 2.55, 95% CI 0.54 to 12.0) with lumiracoxib relative to placebo.¹²⁹ The number of events, however, was low, with only five myocardial infarctions among 1375 patients in the lumiracoxib arms (0.4%).

GI and CV Safety: Comparison of NSAIDs

Partially selective NSAIDs. Evidence that meloxicam, nabumetone, and etodolac prevent ulcer complications is weaker than that for coxibs. Meloxicam is the most widely studied of the three drugs and was generally associated with no advantage in GI protection relative to other partially-selective and non-selective NSAIDs or non-use.^{143, 178-185} Evidence for nabumetone and etodolac is sparse and insufficient to make reliable judgments about comparative GI and CV safety.

Meloxicam. Risks of serious ulcer complications (perforation, bleeding, or obstruction) and/or MI were reported in one clinical trial of meloxicam¹⁷⁹ and three observational studies.^{143, 180, 182} In the single, poor-quality (non-randomized and non-blinded) trial, meloxicam was not associated with significant differences in rates of GI hemorrhage at 6 months relative to other NSAIDs (RR 0.32; 95% CI 0.06, 1.63) in 4,526 rheumatoid arthritis patients seen by family or internal medicine physicians in Germany between August 1996 and July 1997.¹⁷⁹ However,

differences in baseline disease severity could have favored the control group, and it is unclear whether the analyses adjusted for such baseline differences. Estimates of GI and CV risk have also been reported in two recent (2004) cohort studies that followed participants for 14 months¹⁸⁰ and 2.4 years.¹⁴³ GI complication-related hospitalizations were similar for meloxicam (0), nabumetone (1, 4.5%), salsalate (1, 5.9%), naproxen (5, 7.9%), and ibuprofen (0) among a cohort of long-term care residents in Indiana (mean age=81.2 years).¹⁸⁰ In a cohort of 59,724 elderly individuals in Quebec, meloxicam (adjusted rate ratio 1.06; 95% CI 0.49, 2.30) and naproxen (1.17; 95% CI 0.75, 1.84) were associated with similar increases in risk of MI relative to non-use.¹⁴³ Meloxicam (RR 1.5; 95% CI 0.1, 17.1), naproxen (RR 1.0; 95% CI 0.3, 3.3), and piroxicam (RR 0.7; 95% CI 0.2, 2.3) were also associated with similar nonsignificant risks of MI relative to diclofenac in a nested case-control study using data from the UK GPRD.¹⁸²

Estimates of GI risk as measured by a composite score that included GI tolerability, PUBs, hospitalization or GI-related death outcomes were reported in a good-quality meta-analysis.¹⁸³ Compared to non-use, the composite GI risk for meloxicam (RR 1.24; 95% CI 0.98, 1.56) was comparable with that of non-selective NSAIDs. Relative risks of GI hospitalizations or GI-related deaths alone were not reported. Composite GI outcome data from cohort studies were also analyzed in this study and suggested higher risk estimates (combined NSAID RR 2.2, 95% CI 1.7, 2.9) than the trials, but the results were not stratified by individual NSAIDs.

Three meta-analyses focussing only on short-term trials reported PUBs (perforation, symptomatic ulcer, or bleeding) associated with meloxicam. The first meta-analysis included 10 trials (seven double-blinded).¹⁸¹ Most of the patients were followed for only 4 weeks, and the dose of meloxicam was 7.5 mg in 4 trials and 15 mg in 6 trials. The meta-analysis did not report absolute event rates, but found that the risk of PUBs was reduced in the meloxicam patients (OR 0.52, 95% CI 0.28-0.96) relative to non-selective NSAIDs. A twelve-week double-blind trial of meloxicam 7.5, 15 or 22.5 mg and diclofenac 75 mg bid in RA patients (n=894) published after this meta-analysis found similar PUB rates (1.1%, 0.5%, 0.6%, and 0%, respectively) in all arms.¹⁷⁸ In a more recent meta-analysis funded by the manufacturer of meloxicam and using manufacturer-held documents from 28 trials, there was a dose-response relationship between meloxicam and PUBs as ascertained by a blinded, external adjudication committee.¹⁸⁶ Meloxicam at 7.5 mg was associated with lower PUB rates during the first 60 days compared to diclofenac, piroxicam, or naproxen, but the 15 mg dose was only associated with lower PUB rates than piroxicam. In a third meta-analysis (not yet published) of three short-term (4- to 6-week) trials, there was no difference in the risk of complicated ulcers (perforations, obstructions and bleeds) associated with meloxicam relative to the non-selective NSAIDs piroxicam (two trials^{47, 52}) and diclofenac (one trial⁴⁹), with a relative risk of 0.50 (95% CI 0.23, 1.12).¹¹⁵

Nabumetone. For nabumetone, a fair-quality meta-analysis of six short-term (3 to 6 months) studies (five published and one abstract) found one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 non-selective NSAID patients; this result was highly statistically significant.¹⁸⁷ The absolute PUB rates were about 2 versus 6 per 1,000 patient-years. For comparison, in a similar meta-analysis of rofecoxib studies, the PUB rates per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs;¹¹⁸ it is not clear why the rates of PUBs were so much lower in the nabumetone trials. There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patients per year vs. 20.3 per 1,000 patients per year). The results of this meta-analysis are not directly comparable to other trials and meta-analyses that reported complicated ulcers as a separate outcome because

symptomatic ulcers were also included. In addition, the methods used to ascertain the endpoints in the trials were not described in enough detail to determine whether they were accurate and applied consistently. Finally, the similarity of the subjects in the efficacy trials to a broader group of NSAID users could not be determined.

Etodolac. We found no trials reporting rates of serious GI complications in patients taking etodolac. In two observational studies, etodolac was not associated with a lower rate of PUBs compared to non-use¹⁸⁴ or naproxen.¹⁸⁸ In another observational study using data from the UK General Practice Database, the adjusted relative risks of PUB compared with non-use ranged from 2.2 (95% CI 0.4, 11.3) for etodolac to 6.2 (95% CI 3.7, 10.1) for piroxicam and overlapped across all NSAIDs studied.¹⁸⁹ When compared to naproxen using historical data from Dallas Veterans Affairs Medical Center records, etodolac had a GI protective effect for all users (RR 0.24, 95% CI 0.09, 0.63) and for NSAID-naïve users (RR 0.18, 95% CI 0.05, 0.61) only when low-dose aspirin was not taken concomitantly.¹⁸⁸

Non-selective NSAIDs - GI safety. Randomized controlled trials¹¹⁵ and observational studies^{11, 190, 191} consistently report that non-selective, non-aspirin NSAIDs are associated with increased risks of serious GI events relative to non-use. There is no clear, consistent evidence that any one non-selective, non-aspirin NSAID is any less risky than another.

Preliminary results (not yet published) from a meta-analysis of randomized controlled trials found that selective COX-2 inhibitors as a class (defined by the investigators as celecoxib, rofecoxib, valdecoxib, lumiracoxib, and meloxicam) were associated with lower risks of complicated ulcers (perforation, obstruction, or bleed) when compared with naproxen (0.34; 95% CI 0.24, 0.48), ibuprofen (0.46; 95% CI 0.30, 0.70), and diclofenac (0.31; 95% CI 0.06, 1.61).¹¹⁵ There were no clear differences among the three non-selective NSAIDs. The validity of these findings, however, cannot be assessed until the full report is published. However, they are consistent with results from a previous meta-analysis in which increased risks of GI complications (major plus minor) were similar for different NSAIDs relative to non-use: indomethacin (RR 2.25; 95% CI 1.01, 5.07), naproxen (RR 1.83; 95% CI 1.25, 2.68), diclofenac (RR 1.73; 95% CI 1.21, 2.46), piroxicam (RR 1.66; 95% CI 1.14, 2.44), tenoxicam (RR 1.43; 95% CI 0.40, 5.14), meloxicam (RR 1.24; 95% CI 0.98, 1.56) and ibuprofen (RR 1.19; 95% CI 0.93, 1.54).¹⁸³

In an earlier, collaborative meta-analysis of cohort and case-control studies published between 1985 and 1994, use of all non-selective NSAIDs were associated with significantly increased risks of peptic ulcer complication hospitalizations relative to non-use.¹⁹⁰ Ibuprofen, at doses used in general practice, was associated with the lowest risk of peptic ulcer complication-related hospitalizations.¹⁹⁰ In a subsequent meta-analysis of cohort and case-control studies published between 1990 and 1999, however, risk of serious GI event-related hospitalizations and specialist visits was dose-dependent, and was no lower for ibuprofen compared to any other non-aspirin, non-selective NSAID when results were stratified by low to medium (RR 2.1, 95% CI 1.6, 2.7) or high dose (RR 5.5, 95% CI 3.0, 10.0) (Table 18).^{184, 191} A more recent review of observational studies published through 2002 also found GI bleeding risk increased for all non-selective NSAIDs, and risk appeared related more to dose than to the specific drug evaluated.¹¹

Table 18. Relative Risk (95% CI) of UGIB* for NSAIDs vs. non-use

	Hernandez-Diaz 2000 ¹⁹¹			Garcia-Rodriguez 2001 ¹⁸⁴
	Dose			Overall
NSAID	Overall	Low-Medium	High	
Diclofenac	3.3 (2.8, 3.9)	3.1 (2.0, 4.7)	3.6 (2.3, 5.6)	4.6 (3.6, 5.8)
Ibuprofen	1.9 (1.6, 2.2)	2.1 (1.6, 2.7)	5.5 (3.0, 10.0)	2.5 (1.9, 3.4)
Indomethacin	4.6 (3.8, 5.5)	3.0 (2.2, 4.2)	6.5 (4.8, 8.6)	5.2 (3.2, 8.3)
Ketoprofen	4.6 (3.3, 6.4)	NR	NR	3.3 (1.9, 5.9)
Naproxen	4.0 (3.5, 4.6)	3.5 (2.8, 4.3)	5.1 (3.8, 6.9)	4.0 (2.8, 5.8)
Piroxicam	6.3 (5.5, 7.2)	5.6 (4.7, 6.7)	6.2 (4.4, 8.7)	6.2 (3.7, 10.1)
Sulindac	3.6 (2.8, 4.7)	NR	NR	NR

*Upper GI tract bleeding/perforation

Non-selective NSAIDs were also associated with an increased risk of serious GI events in more recent observational studies. Ibuprofen (Odds Ratio 1.42, 95% CI 1.27, 1.59), diclofenac (OR 1.96; 95% CI 1.78, 2.15) and naproxen (OR 2.12, 95% CI 1.73, 2.15) were all associated with increased risks of GI hemorrhage, perforation, surgery or undefined uncomplicated events relative to non-use in a case-control study of the UK General Practice Research Database.¹³⁸ Odds ratios for upper GI events resulting in hospitalization associated with NSAIDs relative to non-use ranged from 3.1 (95% CI 2.0, 4.9) for ibuprofen to 24.7 (95% CI 8.0, 77.0) for ketorolac based on data from 10 hospitals in Spain using a case-control design.¹⁴¹

Non-selective NSAIDs – CV Safety

Randomized controlled trials. Evidence regarding the comparative risk of serious CV events for non-selective NSAIDs is more limited than the evidence for selective COX-2 inhibitors. In particular, long-term clinical trials are lacking. A recent, fair-quality meta-analysis by Kearney and colleagues of 91 trials (mostly ranging from 4 to 13 weeks in duration) evaluated risks with any non-selective NSAID (33,260 person-years of exposure) compared to any COX-2 inhibitor (23,325 person-years of exposure).¹²⁹ Most of the trials evaluated naproxen (42 trials), ibuprofen (24 trials), and diclofenac (26 trials); only 7 evaluated other non-selective NSAIDs. Generalizability to usual practice could be limited because the majority of the trials evaluated higher than standard doses of NSAIDs. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. Other characteristics of this meta-analysis are discussed in more detail in the section on cardiovascular risks associated with rofecoxib.

Table 19 shows estimates of risk for different cardiovascular outcomes with COX-2 inhibitors relative to non-selective NSAIDs. Risk of myocardial infarction was similar with COX-2 inhibitors and non-naproxen NSAIDs, but about two-fold greater for COX-2 inhibitors compared to naproxen (0.6% or 99/16360 vs. 0.3% or 30/10,978, RR 2.04, 95% CI 1.41 to 2.96). This is equivalent to about one additional myocardial infarction for every 301 patients treated for one year with a COX-2 inhibitor instead of naproxen. COX-2 inhibitor use was also associated with a lower risk of stroke relative to non-naproxen NSAIDs (RR 0.62, 95% CI 0.41 to 0.95). In subgroup analyses of specific non-selective NSAIDs (ibuprofen, diclofenac, other non-selective NSAIDs), the difference in stroke risk was only observed with diclofenac, which was usually evaluated at high doses (RR 0.48, 95% CI 0.27 to 0.83). There was insufficient data to analyze the effects of lower doses on estimates of risk.

Table 19. Rate Ratios (95% CI)*: COX 2 inhibitor relative to non-selective NSAID¹²⁹

NSAID group	Vascular events	Myocardial Infarction	Stroke	Vascular Death
Any non-selective NSAID	1.16 (0.97 to 1.38)	1.53 (1.19 to 1.97), p=0.0009	0.83 (0.62 to 1.12)	0.97 (0.69 to 1.35)
Any non-naproxen, non-selective NSAID	0.88 (0.69 to 1.12)	1.20 (0.85 to 1.68)	0.62 (0.41 to 0.95), p=0.03	0.67 (0.43 to 1.06)
Naproxen	1.57 (1.21 to 2.03)	2.04 (1.41 to 2.96), p=0.0002	1.10 (0.73 to 1.65)	1.47 (0.90 to 2.40)

*Rate ratios below 1 favor COX 2 inhibitors and rate ratios above 1 favor NSAIDs

Kearney and colleagues found insufficient data to directly estimate risks of non-selective NSAIDs from placebo-controlled trials. Indirect analyses (based on trials of non-selective NSAIDs versus COX-2 inhibitors and trials of COX-2 inhibitors versus placebo) suggest an increased risk of vascular events with ibuprofen (RR 1.51, 95% CI 0.96 to 2.37) and diclofenac (RR 1.63, 95% CI 1.12 to 2.37) relative to placebo, but not with naproxen (RR 0.92, 95% CI 0.67 to 1.26). However, indirect analyses should be interpreted with caution because they can give discrepant results compared to head-to-head comparisons.¹⁹²

In December 2004, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) was suspended in part because of an "apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo."¹¹¹ However, further details from the ADAPT trial have not yet become available.

Observational studies—naproxen. The risk of MI and other cardiovascular events associated with various non-selective NSAIDs has been evaluated in numerous observational studies. Naproxen has been the most extensively studied non-selective NSAID because of interest generated after the results of the VIGOR trial were published. In order to assess the proposed hypothesis that naproxen is protective against myocardial infarction (rather than rofecoxib causing additional myocardial infarctions), authors of a meta-analysis of randomized controlled trials of rofecoxib also analyzed 11 observational studies of naproxen (four based on the General Practice Research Database).¹²⁴ Compared with non-naproxen NSAIDs, naproxen was associated with a small cardioprotective effect (OR 0.86, 95% CI 0.75 to 0.99). The modest cardioprotective effect would not completely explain the 80% reduction in risk with naproxen compared with rofecoxib observed in the VIGOR trial. In addition, meta-regression analyses indicated that the funding source largely explained between-study heterogeneity. Specifically, Merck-funded studies of naproxen reported larger cardioprotective effects.

An FDA review of four observational studies of naproxen reporting a cardioprotective effect illustrate some difficulties in interpreting the results.¹⁴⁸ In a study by Rahme and colleagues, current exposure to naproxen was associated with a lower risk of acute MI compared with exposure to other NSAIDs (OR 0.79, 95% CI 0.63 to 0.99).¹⁹³ However, when the FDA reviewer re-analyzed the data to compare current exposure to naproxen to non-use of NSAIDs, naproxen was associated with a *higher* risk (OR 1.28, 95% CI 1.10 to 1.49).¹⁴⁸ Although the FDA re-analysis was not adjusted for confounders, examination of adjusted and unadjusted results in the paper suggests that the effects of adjusting would be minor. A study by Kimmel and colleagues found naproxen associated with a lower risk of MI compared with non-use (OR 0.48, 95% CI 0.28 to 0.82), but the results were susceptible to participation bias (about 50% of cases and controls participated) and recall bias (exposure determined by telephone interviews rather than by using pharmaceutical databases or other sources).¹⁹⁴ The third study, by Watson

and colleagues, reported a lower risk of thromboembolic cardiovascular events with current use of naproxen versus non-use (OR 0.61, 95% CI 0.39 to 0.94), but did not adequately control for baseline cardiovascular risk (it used an unvalidated composite measure of risk).¹⁹⁵ Further, when the endpoint of MI alone rather than the composite endpoint of thromboembolic cardiovascular events (which included subdural hematoma, subarachnoid hemorrhage, ischemic stroke, sudden death, or MI) was evaluated, the reduction in risk was not significant (OR 0.57, 95% CI 0.31 to 1.06). Finally, a study by Solomon and colleagues reported a lower risk of MI with use of naproxen within 6 months of an acute MI (OR 0.84, 95% CI 0.72 to 0.98).¹⁹⁶ However, the risk was reduced to a similar degree when the naproxen prescription had run out between 61 and 180 days earlier. Unless naproxen exerts a long-term cardioprotective effect (which is thought to be highly unlikely), these findings are suggestive of underlying selection bias—in other words, persons receiving naproxen were at lower risk for cardiovascular events, and adjustment for known confounders did not eliminate this bias.

In four other recent observational studies (not included in the Juni systematic review) evaluating cardiovascular risk, naproxen was not associated with a cardioprotective effect relative to non-use (Table 20).^{143, 146, 149, 155, 160} However, naproxen was also not clearly associated with an increased risk of myocardial infarction. None of these studies received pharmaceutical industry funding. The FDA review also included two other unpublished studies (Ingenix and MediCal studies) that found no cardioprotective benefit associated with naproxen.¹⁴⁸

Table 20. Risk of myocardial infarction associated with naproxen in recent observational studies not included in the Juni meta-analysis

Study	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴⁶	1.27 (1.01 to 1.60)
Levesque, 2005 ¹⁴³	1.17 (0.75 to 1.84)
Johnsen, 2005 ¹⁴⁹	1.50 (0.99 to 2.29)
Andersohn 2006 ¹⁵⁵	1.16 (0.86 to 1.58)

Overall, the general conclusion from observational studies of a modest decrease in cardiovascular risk associated with naproxen relative to other NSAIDs appears consistent with a systematic review of RCTs.¹²⁹ On the other hand, protective cardiovascular effects of naproxen relative to non-use observed in some observational studies usually appear to be explainable by issues related to study design or analysis. More recent, high-quality observational studies are mostly consistent with a neutral cardiovascular effect of naproxen relative to non-use.

Observational studies—non-naproxen NSAIDs. Results from observational studies regarding the cardiovascular risk associated with non-naproxen, non-selective NSAIDs are mixed. Non-selective NSAIDs as a class and individual NSAIDs have not been consistently associated with increased risks. Results from recent observational studies from the COX-2 era are summarized in Table 21.

Table 21. Risk of myocardial infarction associated with non-selective, non-naproxen NSAIDs

Study	Drug	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴⁶	Ibuprofen	1.24 (1.11 to 1.39)
	Diclofenac	1.55 (1.39 to 1.72)
	Other non-selective, non-naproxen NSAIDs	1.21 (1.02 to 1.44)
Graham, 2005 ¹⁶⁰	Non-selective, non-naproxen NSAIDs	1.13 (1.01 to 1.27)
Levesque, 2005 ¹⁴³	Non-selective, non-naproxen NSAIDs	1.00 (0.73 to 1.37)
Johnsen, 2005 ¹⁴⁹	Non-selective, non-naproxen NSAIDs	1.50 (0.99 to 2.29)
Garcia Rodriguez, 2004 ¹⁸⁵	Ibuprofen	1.06 (0.87 to 1.29)
	Diclofenac	1.18 (0.99 to 1.40)
	Ketoprofen	1.08 (0.59 to 1.96)
	Piroxicam	1.25 (0.69 to 2.25)
	Indomethacin	0.86 (0.56 to 1.32)
	Other non-selective, non-naproxen NSAIDs	0.89 (0.63 to 1.25)
Mamdani, 2003 ¹⁴⁷	Non-selective, non-naproxen NSAIDs	1.2 (0.9 to 1.4)
Ray, 2002 ¹⁵¹	Ibuprofen	0.91 (0.78 to 1.06)
Solomon, 2002 ¹⁹⁶	Ibuprofen	1.02 (0.88 to 1.18)
Watson, 2002 ¹⁹⁵	Ibuprofen	0.74 (0.35 to 1.55)
	Diclofenac	1.68 (1.14 to 2.49)
Andersohn, 2006 ¹⁵⁵	Ibuprofen	1.00 (0.83, 1.21)
	Diclofenac	1.36 (1.17, 1.58)
Schlienger 2002 ¹⁹⁷	Ibuprofen	1.17 (0.87, 1.58)
	Diclofenac	1.38 (1.08, 1.77)
	Piroxicam	1.65 (0.78, 3.49)
	Ketoprofen	1.39 (0.77, 2.51)
	Indomethacin	1.03 (0.58, 1.85)
	Flurbiprofen	2.26 (0.93, 5.46)

In April 2005, after reviewing the available observational data, the FDA issued a Public Health Advisory stating, “Long-term controlled clinical trials have not been conducted with most of these (non-selective) NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and non-selective NSAIDs with the data available. All sponsors of non-selective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk.”¹⁹⁸ The FDA also required labeling changes to both prescription and non-prescription non-selective NSAIDs warning about potential cardiovascular risks.

Aspirin. Aspirin is known to be protective against occlusive vascular events because of its irreversible antiplatelet effects. In a collaborative meta-analysis of 65 randomized controlled trials of aspirin for prophylaxis against thrombotic events, any dose of aspirin reduced the risk of vascular events by an average of 23% (standard error 2).¹⁹⁹ The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg/day, but in trials that directly compared higher and lower doses, there were no significant differences. Again, the populations evaluated in these trials probably varied substantially from trials of

patients with arthritis.

In fact, randomized controlled trials assessing the risk of upper GI bleeding with aspirin have mainly been conducted in populations receiving aspirin as prophylaxis for thrombotic events. It is for this reason that the populations evaluated in these trials may differ on risk factors for bleeding compared to patients who take aspirin for arthritis, as well as being at higher cardiovascular risk. Randomized controlled trials²⁰⁰ and observational studies generally reported that aspirin increases risk of serious GI events relative to placebo or non-use,^{138, 190, 200, 201} but at a rate similar to that of other non-selective NSAIDs.^{138, 189, 190} In these studies, the dose of aspirin varied widely and was generally lower (50 mg to 1500 mg daily) than the doses considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods. In a good-quality meta-analysis of 24 randomized trials with nearly 66,000 participants, the risk of gastrointestinal hemorrhage was 2.47% with aspirin compared with 1.42% with placebo (OR 1.68, 95% CI 1.51 to 1.88), based on an average of 28 months therapy.²⁰⁰ There was no relation between gastrointestinal hemorrhage and dose in this study. Further, modified release formulations did not attenuate the risk for bleeding. In a more recent, fair-quality meta-analysis of 31 randomized trials with over 190,000 subjects, the risk of major bleeding was 1.56% with doses <100 mg, 1.54% with 100-200 mg, and 2.29% with >200.²⁰² Although the difference between doses >200 and <100 was statistically significant, the absolute differences are small.

Systematic reviews of cohort and case-control studies published between 1985 and 2001 reported similar findings,^{189, 190, 201} except that the most recent review found a dose-response relationship between aspirin and risk of bleeding.¹⁸⁹ However, aspirin was associated with upper GI bleeding even at low doses. Findings from a recent UK practice-based case-control study (9,407 cases) found that compared with non-use, aspirin was associated with an increased risk of complicated or uncomplicated adverse GI events (odds ratio 1.60, 95% CI 1.49, 1.72) similar to that of naproxen, diclofenac, and ibuprofen.¹³⁸ These findings are consistent with a systematic review of observational studies that only assessed peptic ulcer-related hospitalizations.¹⁹⁰

Salsalate. Serious GI event rates (bleeding, perforation, obstruction) associated with salsalate were only reported in one cohort of long-term care residents in Indiana. The number of cases of GI-related hospitalizations associated with salsalate (1, 5.9%) after 14 months was similar to that of other selective and non-selective NSAIDs (cited in partially selective NSAID section above).¹⁸⁰

Other Adverse Events Associated with Selective and Non-Selective NSAIDs

Mortality. Large clinical trials have not shown differences in mortality rates between different NSAIDs. In VIGOR, for example, mortality was 0.5% with rofecoxib versus 0.4% with naproxen,¹⁹ and in CLASS mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.⁹⁴ A meta-analysis that included unpublished company clinical trial data (including CLASS) found no significant difference in rates of death in patients randomized to celecoxib compared with non-selective NSAIDs, though there were few events (0.03% or 6/18,325 in the celecoxib arms versus 0.11% or 14/12,685 in the NSAID arms).⁶² In one retrospective cohort study of Saskatchewan health-services databases that followed patients from 6 months following prescription until death, nabumetone was associated with significantly lower rates of all-cause mortality compared with diclofenac (adjusted odds ratio 1.96; 95% CI

1.25, 3.07) and naproxen (adjusted odds ratio 2.95, 95% CI 1.88, 4.62).²⁰³ However, we found no other studies replicating this finding.

Hypertension, CHF, edema, and renal function. All non-selective NSAIDs appear to be associated with increases in blood pressure. However, evidence regarding differential effects of specific NSAIDs is somewhat conflicting. Two meta-analyses of placebo-controlled trials have compared the effects of different non-selective NSAIDs on blood pressure increases.^{204, 205} One meta-analysis found that non-selective NSAIDs raised mean blood pressure by an average of about 5.0 mm Hg (95% CI, 95% CI 1.2 to 8.7).²⁰⁴ Piroxicam produced the most marked elevation in blood pressure.²⁰⁴ By contrast, the other meta-analysis found that piroxicam and ibuprofen had negligible effects on blood pressure, and that indomethacin and naproxen were associated with the largest increases.²⁰⁵ In both meta-analyses, aspirin and sulindac were associated with minimal hypertensive affect. In an analysis of head-to-head trials, there were no significant differences between indomethacin and sulindac (10 trials), indomethacin and salicylate (one trial), diclofenac and sulindac (one trial), ibuprofen and sulindac (one trial), and naproxen and sulindac (three trials).²⁰⁴ The reliability of the meta-analyses is compromised by a high likelihood of publication bias; more than half of published NSAID trials did not report hypertension rates as an outcome.²⁰⁵

Several studies have reported hypertension outcomes for selective COX-2 inhibitors compared to non-selective NSAIDs. One fair-quality meta-analysis found COX-2 inhibitors as a class (celecoxib, rofecoxib, and etoricoxib) not associated with an increased risk of developing hypertension compared to non-selective NSAIDs (RR 1.25, 95% CI 0.87 to 1.78). Pooling evidence on blood pressure effects from various selective and non-selective NSAIDs may be misleading, however, because of potential differences between COX-2 inhibitors, dissimilarities in dosing and comparator drugs, and a high likelihood of publication bias affecting conclusions.

Evidence regarding risks of hypertension with rofecoxib is somewhat mixed. A good-quality Cochrane review found that rates of edema and hypertension were not reported in most trials.⁷⁷ For rofecoxib versus nabumetone, there was no difference in the rate of hypertension in two trials (pooled RR 1.46, 95% CI 0.53 to 4.12). A meta-analysis of nine phase IIb/III osteoarthritis trials sponsored by the manufacturer of rofecoxib found that rofecoxib 12.5 mg and 25 mg daily were associated with higher rates of lower extremity edema, congestive heart failure, and hypertension than placebo.²⁰⁶ Edema and hypertension rates were similar between the rofecoxib (1.2 per 100 patient-months) and ibuprofen (1.3 per 100 patient-months) groups but somewhat higher than in the diclofenac group (0.3 per 100 patient months). Discontinuations due to these adverse events were rare: of 2,829 randomized to rofecoxib, seven discontinued due to edema, two due to hypertension, and one due to CHF. However, five of the nine trials were shorter than 6 weeks in duration, so these rates may not be representative of results in long-term users. A more recent fair-quality meta-analysis of arthritis trials found rofecoxib associated with a higher risk of developing hypertension compared to either placebo (RR 2.63, 95% CI 1.42 to 4.65) or non-selective NSAIDs (RR 1.78, 95% CI 1.17 to 2.69).²¹

Results of large, longer-term trials appear to be consistent with an increased risk of hypertension with rofecoxib compared to either placebo or non-selective NSAIDs. In VIGOR (N=8,076) rofecoxib 50 mg daily was associated with a higher risk of developing hypertension compared to naproxen (RR 1.69, 95% CI 1.42-1.99) and a higher risk of discontinuation due to hypertension-related adverse events (RR 4.67, 95% CI 1.93 to 11.28).¹¹⁴ In addition, 19 patients developed CHF-related adverse events during 4,047 patient-years of exposure, compared with

nine patients during 4,029 patient-years of exposure to naproxen (RR 2.11, 95% CI 0.96 to 4.67). In the long-term APPROVe polyp prevention trial, hypertension (RR 2.02, 95% CI 1.71 to 2.38), edema (RR 1.57, 95% CI 1.17 to 2.10), and heart failure or pulmonary edema (RR 4.61, 95% CI 1.50 to 18.83) were all increased with rofecoxib 25 mg qD compared with placebo.¹³²

In contrast to rofecoxib, several meta-analyses of celecoxib suggest no increased risk of hypertension or heart failure compared to non-selective NSAIDs. In fact, a recent fair-quality meta-analysis found celecoxib (dose not specified) not associated with an increased risk of hypertension compared to either placebo (RR 0.81, 95% CI 0.13 to 5.21) or non-selective NSAIDs (RR 0.82, 95% CI 0.68 to 1.00).²¹ On the other hand, a Pfizer-funded meta-analysis submitted to the FDA found that, for celecoxib (any dose), the risk of developing hypertension was higher than placebo (1.1% vs. 0.7%, $p=0.023$) but lower than the non-selective NSAIDs (1.5% vs. 2.0%, $p=0.002$).¹³⁵ Heart failure was more frequent in patients taking celecoxib than those taking placebo (13 of 8,405 versus one of 4,057, $p=0.046$), though not compared with non-selective NSAIDs (0.1% vs. 0.2%, $p=0.056$). A third meta-analysis, funded in part by the manufacturer, reported similar findings for risk of hypertension (celecoxib vs. non-selective NSAID RR 1.1, 95% CI 0.90 to 1.3) and heart failure (celecoxib vs. non-selective NSAID RR 0.70, 95% CI 0.43 to 1.1).⁶² Most of the trials included in the meta-analyses were short-term and only one meta-analysis⁶² evaluated the quality of the trials. However, results from large trials of celecoxib are consistent with the meta-analyses. In CLASS (N=8,059), celecoxib was associated with a similar rate of hypertension (new-onset and aggravated pre-existing) compared with diclofenac (2.7% vs. 2.6%), but a significantly lower rate than ibuprofen (2.7% vs. 4.2%).¹⁰⁵ CHF rates were similar in patients randomized to celecoxib versus either ibuprofen or diclofenac (0.3% vs. 0.3%). In the shorter-term SUCCESS-I trial (N=13,274), rates of hypertension were similar with celecoxib 100 or 200 mg bid compared to either diclofenac or naproxen (RR 0.86, 95% CI 0.62 to 1.20).²¹ The APC polyp prevention trial found celecoxib associated with significant systolic blood pressure elevations compared to placebo at 1 and 3 years at either 200 mg twice daily (2.0 mm Hg at 1 year and 2.6 mm Hg at 3 years) and 400 mg twice daily (2.9 mm Hg at 1 year and 5.2 mm Hg at 3 years).¹⁰⁹ By contrast, the PreSAP polyp prevention trial found no difference in systolic blood pressure elevations between celecoxib 400 mg once daily and placebo.¹⁰⁹ The APC polyp prevention trial found no difference in rates of heart failure between patients randomized to celecoxib versus those randomized to placebo, though event rates were low (five cases of heart failure among 1,356 subjects).¹⁰⁸

Direct evidence on comparative blood pressure effects of celecoxib compared to rofecoxib is more limited. A good-quality Cochrane review found no difference in rates of clinically significant increases in blood pressure or edema with rofecoxib versus celecoxib in three head-to-head trials of average-risk populations with osteoarthritis.⁷⁷ Another meta-analysis that used unpublished clinical trial reports also found no difference in risk of hypertension or aggravated hypertension in patients on celecoxib versus rofecoxib (RR 0.75, 95% CI 0.52 to 1.1).⁶² On the other hand, in contrast to the Cochrane review, this meta-analysis found a lower rate of edema with celecoxib versus rofecoxib (5 trials, RR 0.72, 95% CI 0.62 to 0.83). A third meta-analysis found rofecoxib associated with a greater risk of developing a clinically important elevation in systolic blood pressure (RR 1.50, 95% CI 1.00 to 2.26), though the difference was not statistically significant.²¹

Three other short-term head-to-head trials of celecoxib and rofecoxib in higher-risk populations (hypertensive, osteoarthritic patients) funded by the manufacturer of celecoxib should be interpreted cautiously because they evaluated doses (rofecoxib 25 mg daily and

celecoxib 200 mg daily) that may not provide equivalent pain relief.^{84, 85, 207} Two 6-week trials of elderly (>65 years) patients with osteoarthritis and on antihypertensive therapy (SUCCESS VI and SUCCESS VII) found that rates of increased systolic blood pressure (>20 mm Hg increase and absolute value >140 mm Hg) were higher in patients randomized to rofecoxib (n=399) compared to celecoxib (n=411): 14.9% vs. 6.9% (p<0.01) in one trial⁸⁵ and 17% vs. 11% (p=0.032) in the other.⁸⁴ However, in one of these trials (SUCCESS VI),⁸⁴ there was an important baseline difference in the proportion of patients who took an ACE inhibitor for hypertension (40% for celecoxib-treated patients versus 29% for rofecoxib-treated patients, p=0.002). This could suggest inadequate randomization, as successful randomization is unlikely to have resulted in such a marked baseline difference. In the third trial (CRESCENT), which enrolled patients with controlled hypertension, diabetes, and osteoarthritis, the proportion that developed ambulatory hypertension (systolic blood pressure >135) was higher with rofecoxib than with celecoxib (30% vs. 16%, p=0.05).²⁰⁷ In the CRESCENT and SUCCESS-VI trials, edema was more common in patients assigned to rofecoxib compared with those assigned to celecoxib (7.7% vs. 4.7%, p<0.05²⁰⁷ and 9.5% vs. 4.9%, p=0.014⁸⁴). Three patients on rofecoxib and two on celecoxib developed heart failure in CRESCENT compared with four versus none in SUCCESS-VI; these differences were not significant. Discontinuations due to these adverse events did not differ.

With regards to renal toxicity, there is little evidence to suggest that selective NSAIDs as a class are safer than non-selective NSAIDs. A systematic review of five small (sample size range 15 to 67), short-term (28 days or less) trials found that selective NSAIDs had similar effects on glomerular filtration rate and creatinine clearance in three trials, and were modestly superior in two.²⁰⁸ The clinical effects of the modest differences observed in the latter two trials are unclear. Another meta-analysis found that celecoxib at 200 to 400 mg was not associated with a greater risk of increase in creatinine greater than 1.3 times the upper limit of normal compared to non-selective NSAIDs (RR 0.78, 95% CI 0.46 to 1.3).⁶²

There is also no clear evidence suggesting that celecoxib is associated with improved renal safety compared with rofecoxib. In the CLASS trial, there was one fewer episode of edema, hypertension, or increased creatinine for every 62 patients treated with celecoxib instead of ibuprofen 800 mg tid or diclofenac 75 bid.⁶⁰ The effects of celecoxib on renal function were also reviewed in a meta-analysis of primarily unpublished data (not including CLASS) that found the overall incidence of renal adverse events similar to that of non-selective NSAIDs.²⁰⁹ In VIGOR, the incidence of adverse events related to renal function (outcome not specifically defined) was similar for the rofecoxib and naproxen groups (1.2% versus 0.9%), with 0.2% discontinuing treatment in each arm because of these events.¹⁹ A meta-analysis of manufacturer's data found rofecoxib associated with an overall incidence of elevations in serum creatinine similar to non-selective NSAIDs.²⁰⁶ Discontinuations due to elevated serum creatinine were rare, and there were no cases of acute renal failure (not defined) associated with rofecoxib.

The risks of hypertension and heart failure with rofecoxib and celecoxib have also been evaluated in several good-quality observational studies. A large case-control study found that rofecoxib users were at significantly increased risk for new-onset hypertension compared with patients taking celecoxib (OR 1.6, 95% CI 1.2 to 2.1).²¹⁰ A retrospective cohort study found rofecoxib associated with an increased risk of admission for heart failure compared with NSAID-non-users (RR 1.8, 95% CI 1.5 to 2.2), though celecoxib was not (RR 1.0, 95% CI 0.8 to 1.3).¹⁶³ Rofecoxib (HR 1.27, 95% CI 1.09 to 1.49) and non-selective NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) were also associated with higher risks of death or recurrent CHF compared with

celecoxib in another study of high-risk patients following a heart-failure admission.²¹¹ In two observational studies, use of non-selective NSAIDs was associated with heart-failure admissions (RR 1.4, 95% CI 1.0 to 1.9)¹⁶³ and newly diagnosed heart failure (adjusted RR 1.6, 95% CI 1.2 to 2.1)²¹² when compared with non-use.

Hepatotoxicity. We identified one systematic review that evaluated rates of aminotransferase elevations, liver-related discontinuations, and other serious hepatic adverse events, including hospitalizations and deaths, in randomized controlled trials of rofecoxib, celecoxib, valdecoxib, meloxicam, diclofenac, naproxen, and ibuprofen in adults with osteoarthritis or rheumatoid arthritis.²¹³ It identified 67 published articles and 65 studies accessible from the FDA archives. Diclofenac (3.55%, 95% CI 3.12% to 4.03%) and rofecoxib (1.80%, 95% CI 1.52% to 2.13%) had higher rates of aminotransferase elevations >3 times the upper limit of normal compared with placebo (0.29%; 95% CI 0.17% to 0.51%) and the other NSAIDs (all < or = 0.43%). However, only diclofenac was associated with a higher rate of liver-related discontinuations than placebo (2.17%, 95% CI 1.78% to 2.64%). Serious complications related to liver toxicity were extremely rare: only one liver-related hospitalization (among 37,671 patients) and death (among 51,942 patients) occurred in a patient on naproxen in the VIGOR trial. There was also a statistically significant difference in elevated (three times above the upper limit of normal) transaminase levels between lumiracoxib (which is chemically related to diclofenac) and naproxen or ibuprofen (HR 3.97, 95% CI 2.96, 5.32) in the large TARGET (N=18,325) trial, though these elevations were reversible upon drug discontinuation.¹⁷⁵

A recent systematic review of seven population-based epidemiological studies of hepatotoxicity with NSAIDs found a similarly low risk of serious hepatic toxicity.²¹⁴ In those studies, the excess risk of liver injury associated with current NSAIDs ranged from 4.8 to 8.6/100,000 person-years of exposure compared with past use. There were zero deaths from liver injury associated with NSAIDs in over 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the U.S., was associated with a higher incidence of serious liver injury compared with other NSAIDs.²¹⁵ None of the other NSAIDs, including celecoxib, were associated with an increased risk of serious liver injury. An earlier review of five population-based studies found sulindac associated with a 5-10 fold higher incidence of hepatic injury compared with other NSAIDs.²¹⁶ Diclofenac was associated with higher rates of aminotransferase elevations compared with users of other NSAIDs, but not with a higher incidence of serious liver disease.

Tolerability: Comparison of NSAIDs

Partially selective NSAIDs. Evidence is mixed regarding the relative tolerability of meloxicam (7.5 mg or 15 mg) compared to non-selective NSAIDs. The meta-analysis of meloxicam studies mentioned earlier found lower rates of any gastrointestinal event (OR 0.64; 95% CI 0.59, 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52, 0.67) compared with NSAIDs, but as mentioned before it included some inadequately blinded studies, which are less reliable for assessing withdrawals and attributing the cause of adverse events.¹⁸¹ The double-blind trial of meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid mentioned earlier²¹⁷ found no significant differences in rates of withdrawals due to adverse events or in incidence of overall and gastrointestinal tolerability.

In the nabumetone meta-analysis, the incidence of GI adverse events was significantly lower on nabumetone compared to non-selective NSAIDs (25.3% vs. 28.2%, $p=.007$), corresponding to

about one fewer event for every 34 patients treated with nabumetone.¹⁸⁷

Numerous randomized controlled trials reported microscopic bleeding or endoscopic outcomes with etodolac. However, we identified no randomized trials or systematic reviews assessing the clinical tolerability of etodolac relative to non-selective NSAIDs.

Non-selective NSAIDs. One Cochrane review evaluated the tolerability of different NSAIDs.⁴¹ The only relatively consistent finding was that indomethacin was associated with higher rates of toxicity than other NSAIDs, but it was not clear if these differences were statistically significant.

Aspirin and salsalate. Five randomized trials have evaluated the efficacy or safety of aspirin or salsalate compared with non-aspirin NSAIDs in patients with arthritis.^{56, 218-221} All were short-term in duration (≤ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only four had osteoarthritis of the hip/knee for every 100 patients with rheumatoid arthritis. Aspirin was associated with higher incidence of overall adverse events than salsalate (70% vs. 40%, $p < 0.05$)⁵⁶ and diclofenac (61% vs. 46%; $p < 0.05$);²¹⁸ these led to higher rates of withdrawals due to adverse events for aspirin compared with diclofenac (23% vs. 6%; $p < 0.05$). Salsalate was associated with a higher incidence of overall adverse events compared to other non-selective NSAIDs in two^{220, 221} of three trials, but the actual rates were not reported.

The overall safety profile of salsalate has also been evaluated in the rheumatoid arthritis population using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) databases. These studies reported summary measures of drug toxicity based on tabulations of mean frequencies of overall adverse events per patient years, weighted by severity, and adjusted for differences in demographic factors. Numerically larger index scores indicate greater levels of toxicity. The summary index score takes into account symptoms from all body systems, laboratory abnormalities, and all-cause hospitalizations.^{201, 222-224} Symptoms were assessed every 6 months using patient self-report in response to open-ended questions. Hospitalization and death data were ascertained from discharge summaries and death certificates. Descriptions of study methods varied, but in general the ARAMIS studies were somewhat vague with regard to patient selection and ascertainment methods; adverse events were not clearly defined or prespecified; exposure duration and length of follow-up were unclear; and adjustments were made only for demographic factors such as age and gender. Because the results of these studies are more subject to recall bias and had other methodological shortcomings, the findings that aspirin, salsalate, and ibuprofen were the least toxic among the NSAIDs studied (Table 22 below) are less convincing than results of more recent observational studies (discussed earlier).

Table 22. Toxicity Index Scores from ARAMIS database studies

Study	Aspirin	Ibuprofen	Salsalate	Others (range)
Fries 1991 ²²²	1.19	1.94	1.28	2.17 (Naproxen) to 3.99 (Indomethacin)
Fries 1993 ²²⁴	1.33	1.89	NR	1.90 (Naproxen) to 2.86 (Tolmetin)
Fries 1996 ²²³	1.77	2.68	2.00	1.63 (Sulindac) to 3.09 (Ketoprofen)
Singh 1997 ²⁰¹	2.25	1.95	1.79	3.29 (Naproxen) to 5.14 (Meclofenamate)

COX-2 vs. NSAID. Two manufacturer-funded meta-analyses^{61, 62} and one good-quality Cochrane review²²⁵ found celecoxib consistently associated with more favorable overall and GI tolerability profiles relative to some, but not all, non-selective NSAIDs in short-term RCTs of

patients with OA/RA (Table 23). Evidence of relative tolerability is less consistent for rofecoxib compared to partially-selective or non-selective NSAIDs in short-term RCTs of patients with OA/RA as reported in one manufacturer-funded meta-analysis,²²⁶ two good-quality Cochrane reviews,^{77, 78} and one other RCT that was not included in the systematic reviews.⁷⁶

Effect size differences between the COX-2 manufacturer-funded analyses and the Cochrane reviews may have been due, in large part, to differences in methods of study selection and statistical analyses. The Cochrane Reviews primarily relied upon electronic database searches for identification of published RCTs evaluating narrow patient populations, and results from each trial were generally presented separately.^{77, 78, 225} Manufacturer-funded meta-analyses relied solely^{62, 226} or in part⁶¹ on internal records to identify studies and presented only pooled estimates of broader populations including OA and RA patients.

Table 23. Tolerability profile of COX-2's vs. NSAIDs in meta-analysis and systematic reviews

Review	AE incidence		Withdrawals	
	Overall	GI-related	Any AE	GI-related
Celecoxib vs. NSAIDs for OA/RA				
<i>Manufacturer-funded meta-analyses</i>				
Deeks 2002 ⁶¹	-	-	RR 0.86 (0.72, 1.04)	RR 0.54 (0.42, 0.71)
Moore 2005 ⁶²	0.96 (0.94, 0.98)	0.84 (0.81, 0.87)	RR 0.86 (0.81, 0.91)	RR 0.75 (0.7, 0.8)
Celecoxib vs. individual NSAIDs for RA				
<i>Gamer 2005a²²⁵ (Cochrane Collaboration Systematic Review)</i>				
<i>Celecoxib vs. Naproxen</i>				
-	-	-	No differences (RR Range: 1.02-1.36)	No differences (RR Range: 0.26-0.61)
<i>Celecoxib vs. Diclofenac</i>				
-	0.75 (0.62, 0.90)	0.95 (0.85, 1.04)	0.54 (0.36, 0.79)	0.36 (0.21, 0.60)
Rofecoxib vs. NSAIDs for OA				
<i>Watson 2000²²⁶ (Manufacturer-funded meta-analysis)</i>				
6-month	-	0.86 (0.78, 0.95)	-	0.68 (0.50, 0.92)
12-month	-	0.88 (0.80, 0.97)	-	0.70 (0.52, 0.94)
<i>Gamer 2005c⁷⁷ (Cochrane Collaboration Systematic Review)</i>				
<i>Rofecoxib vs. Diclofenac</i>				
No differences (RR range: 0.98-1.01)	-	-	12.5 mg: 0.71 (0.52, 0.97) 25 mg: 0.70 (0.51, 0.95)	-
<i>Rofecoxib vs. Ibuprofen</i>				
NS (RR range: 0.98-1.04)	-	-	↓ risk in 2 of 3 RCTs	No differences in 3 of 4 RCTs
<i>Rofecoxib vs. Naproxen</i>				
No differences	0.55 (0.42, 0.73)	-	No differences	↓ risk in 2 of 3 RCTs
<i>Rofecoxib vs. Nabumetone</i>				
NR	NR	-	No differences	No differences
Rofecoxib vs. Naproxen in RA				
<i>Gamer 2005b⁷⁸ (Cochrane Collaboration Systematic Review)</i>				
-	-	-	1.02 (0.92, 1.12)	0.74 (0.64, 0.85)

A manufacturer-funded meta-analysis found that tolerability of valdecoxib relative to NSAIDs appeared to be time-dependent.²²⁷ Significant increases in overall adverse event incidence (RR 1.1; 95% CI 1.04, 1.2) and incidence of GI adverse events (RR 1.4; 95% CI 1.2, 1.6) for valdecoxib relative to NSAIDs did not lead to increased risk of discontinuation in RCTs

of 6-12 weeks' duration. By 12-26 weeks, however, valdecoxib was associated with significantly lower rates of overall adverse events (RR 0.9; 95% CI 0.85, 0.93) and GI-related adverse events (RR 0.7; 95% CI 0.7, 0.8) relative to non-selective NSAIDs, as well as lower rates of discontinuation due to any adverse event (RR 0.9; 95% CI 0.85, 0.93) and due to GI-related adverse events (RR 1.4; 95% CI 1.2, 1.6).

Comparison between COX-2 inhibitors. Incidence of and withdrawals due to overall or GI-related adverse events were similar for celecoxib and rofecoxib across a manufacturer-funded meta-analysis⁶² and a good-quality Cochrane review.⁷⁷ The manufacturer-funded meta-analysis reported that rofecoxib and celecoxib were associated with similar risks of any adverse event (RR 0.97; 95% CI 0.84, 1.1), any GI-related adverse event (RR 0.87, 95% CI 0.74, 1.03), and GI-adverse event discontinuation (RR 0.7; 95% CI 0.5, 1.2) using data from five 6- to 12-week RCTs of patients with either OA or RA.⁶² The Cochrane review of rofecoxib for osteoarthritis⁷⁷ found no differences for either the total number of withdrawals (RR 0.93, 95% CI 0.76 to 1.14) or the number of withdrawals due to adverse events (RR 1.03, 95% CI 0.77 to 1.39) in five trials that compared celecoxib to rofecoxib.

Acetaminophen. We identified four systematic reviews that evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or non-selective) for osteoarthritis.²²⁸⁻²³¹ The studies generally met all criteria for good-quality systematic reviews, except that three²²⁹⁻²³¹ did not provide sufficient detail about trials that were excluded. The overall conclusion from the reviews was that NSAIDs are modestly superior to acetaminophen for general or rest pain (Table 24). For pain on motion and overall assessment of clinical response, NSAIDs also appeared modestly superior, though the differences were not always statistically significant.^{229, 230} Only two reviews assessed functional disability; neither found clear differences.^{229, 230}

Table 24. Pain relief in systematic reviews of acetaminophen versus NSAID

Systematic review	Date of last search	Number of head-to-head trials included	Main results for outcome of general or rest pain
Towheed, 2005 ²²⁹	Through 8/02	5 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (SMD 0.32, 95% CI 0.08 to 0.56) and HAQ pain (SMD 0.27, 95% CI 0.05 to 0.48)
Zhang, 2004 ²³¹	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDs superior using WOMAC scale (pooled ES 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)
Lee, 2004 ²²⁸	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference -6.33, 95% CI -9.24 to -3.41)
Wegman, 2004 ²³⁰	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (standardized mean difference 0.33, 95% CI 0.15 to 0.51)

The risk of adverse events with acetaminophen versus NSAIDs was assessed in three systematic reviews (Table 25).^{228, 229, 231} In two reviews, there were no differences in withdrawal due to any adverse event.^{229, 231} However, acetaminophen was associated with fewer gastrointestinal side effects compared with non-selective NSAIDs (though not compared with coxibs)^{229, 231} and fewer withdrawals due to gastrointestinal adverse events.²²⁹

Table 25. Adverse events in systematic reviews of acetaminophen versus NSAID

Systematic review	Withdrawal due to adverse events	GI adverse events
Towheed, 2005 ²²⁹	No difference (8% vs. 9%)	Withdrawal due to GI adverse event Naproxen or ibuprofen vs. acetaminophen: RR 2.15 (95% CI 1.05 to 4.42) Any GI adverse event Non-selective NSAID vs. acetaminophen: RR 2.24 (95% CI 1.23 to 4.08) Coxib vs. acetaminophen: RR 0.96 (95% CI 0.57 to 1.61)
Zhang, 2004 ²³¹	Not reported	GI discomfort Non-selective NSAID vs. acetaminophen: RR 1.39 (95% CI 1.07 to 1.80) Coxib vs. acetaminophen: RR 0.65 (95% CI 0.17 to 2.52)
Lee, 2004 ²²⁸	NSAID vs. acetaminophen: OR 1.45, 95% CI 0.93 to 2.27)	Not reported

Results of recent, good-quality randomized trials (not included in any of the systematic reviews) were consistent with the systematic reviews. One two-week trial (N=222) found ibuprofen 1,200 mg/day more effective than paracetamol 3,000 mg/day for pain relief ($p<0.005$) and functional disability using WOMAC scores (-20.8 versus -13.4, $p<0.001$).²³² Two cross-over trials of identical design (N=524 and 556) found celecoxib modestly superior to acetaminophen for WOMAC scores (difference in WOMAC score improvements ranged from 2.8 to 5.0 points on a 100-point scale), visual analogue pain scales (mean difference in scores ranged from 3.5 to 7.7 mm on a 100 mm scale), and patient preferences (53% and 50% favored celecoxib, versus 24% and 32% favored acetaminophen).²³³ In all three trials, tolerability and safety were equivalent.

Clinical trials of acetaminophen have not been large enough to assess serious but less common complications such as PUB, myocardial infarction, acute renal failure, or hypertension. However, observational studies provide some additional information about the safety of acetaminophen relative to NSAIDs. A good-quality nested case-control study of 1,197 cases and 10,000 controls from a population-based cohort of 458,840 persons in the General Practice Research Database found current acetaminophen use associated with a lower risk for symptomatic peptic ulcer (adjusted RR 1.9, 95% CI 1.5 to 2.3) than NSAID use (adjusted RR 4.0, 95% CI 3.2 to 5.1) when each was compared with non-use.²³⁴ There was no clear relationship between higher acetaminophen dose and increased risk for symptomatic ulcers. An earlier analysis on the same database also found current acetaminophen use associated with a lower risk for upper gastrointestinal bleeds or perforations (adjusted RR 1.3, 95% CI 1.1 to 1.5) than current NSAID use (adjusted OR 3.9, 95% CI 3.4 to 4.6), each compared with non-use.¹⁸⁴ A retrospective cohort study of elderly patients found that patients using lower doses of acetaminophen (<2,600 mg/day) had lower rates of GI events (defined as GI-related hospitalizations, ulcers, and dyspepsia) compared with users of NSAIDs (RR 0.73, 95% CI 0.67 to 0.80 for 1,951 to 2,600 mg/day), but the risks were similar at higher doses (RR 0.93 to 0.98).²³⁵ Although GI hospitalization rates were not reported separately, the authors noted that dyspepsia was responsible for most of the increase in GI events in the high-dose acetaminophen groups. A meta-analysis on individual patient data from three earlier retrospective case-control studies (2472 cases) was consistent with the above studies.²³⁶ It found acetaminophen associated

with a minimal increase in the risk for serious upper gastrointestinal bleeding (OR 1.2, 95% CI 1.1 to 1.5). By contrast, non-selective NSAIDs were associated with higher risks, though estimates of risk varied considerably for different NSAIDs (OR 1.7 for ibuprofen to 34.9 for ketoprofen).

No randomized trial has evaluated the association between acetaminophen use and myocardial infarction or other thromboembolic cardiovascular events. However, a recent analysis from the large, prospective Nurses' Health Study found heavy use of acetaminophen (more than 22 days/month) associated with an increased risk of cardiovascular events (RR 1.35, 95% CI 1.14 to 1.59) similar to that with heavy use of NSAIDs (RR 1.44, 95% CI 1.27 to 1.65).²³⁷ Dose- and frequency-dependent effects were both significant.

The association between renal failure and acetaminophen use has been evaluated in several case-control studies. Interpretation of these studies, however, is difficult because many had important flaws (such as failure to identify patients early enough in the course of their disease to insure that the disease had not led to a change in the use of analgesics, failure to specify diagnostic criteria, failure to adjust for the use of other analgesics, incompleteness of data on exposure, and use of proxy respondents) in the collection or analysis of data.²³⁸ The largest (926 cases) case-control study was designed to try to avoid many of these flaws.²³⁹ It found regular use of acetaminophen associated with an increased risk for chronic renal failure (Cr >3.8 for men and >3.2 for women) compared with non-use (OR 2.5, 95% CI 1.7 to 3.6). Use of NSAIDs was not associated with an increased risk (OR 1.0). A prospective cohort study of 1,697 women in the Nurses' Health Study found increased lifetime acetaminophen exposure associated with a higher risk of decline in glomerular filtration rate of 30% or greater ($p < 0.001$), though NSAIDs were not ($p = 0.88$).²⁴⁰ The absolute risk of renal function decline, however, was modest, even in women reporting high amounts of lifetime acetaminophen use. Compared with women consuming less than 100 g of cumulative acetaminophen, the odds of a decline in GFR of at least 30 mL/min per 1.73 m² for women consuming more than 3,000 g was 2.04 (95% CI, 1.28 to 3.24). By contrast, analyses of men in the Physicians' Health Study found no association between acetaminophen or NSAIDs and change in kidney function.^{241, 242}

The risk of heart failure associated with acetaminophen has not been well studied. In a single study using the General Practice Research Database, current use of acetaminophen was associated with a higher risk of newly diagnosed heart failure compared with non-use (RR 1.33, 95% CI 1.06 to 1.67), though the risk was lower compared with current use of NSAIDs (RR 1.59, 95% CI 1.23 to 2.05).²¹²

The risk of hypertension has been evaluated using data from the Nurses' Health Studies²⁴³⁻²⁴⁵ and the Physicians' Health Study.²⁴⁶ In the Nurses' Health Studies, acetaminophen and NSAIDs were associated with similar increases in risk of incident hypertension (Table 26). In the Physicians' Health Study, on the other hand, there was no association between NSAID or acetaminophen use and hypertension.

Table 26. Incidence of hypertension in the Nurses' Health Study and Physicians' Health Study according to use of acetaminophen or NSAIDs

Study	Acetaminophen use versus non-use: odds ratio	NSAID use versus non-use: odds ratio
Nurses' Health Study I (women 51 to 77 years old) ²⁴³	1.93 (1.30 to 2.88)	1.78 (1.21 to 2.61)
Nurses' Health Study II (women 34 to 53 years old) ²⁴³	1.99 (1.39 to 2.85)	1.60 (1.10 to 2.32)
Physicians' Health Study ²⁴⁶	1.08 (95% CI 0.87 to 1.34)	1.05 (95% CI 0.89 to 1.24)

Although overdoses with acetaminophen can lead to potentially life-threatening hepatotoxicity, it is not clear if hepatotoxicity is associated with therapeutic doses in patients without underlying liver disease.¹⁶ We identified no studies comparing the incidence of hepatotoxicity with therapeutic doses of acetaminophen and NSAIDs. We also identified no studies comparing the incidence of myocardial infarctions in persons using acetaminophen compared with NSAIDs.

Glucosamine and Chondroitin

Data regarding the comparative efficacy of glucosamine versus NSAIDs in patients with osteoarthritis are mixed. The most promising results have been observed in trials sponsored by Rotta Research Laboratories (based in Europe), which manufactures pharmaceutical grade glucosamine not available in the U.S. Because the content and purity of over-the-counter glucosamine preparations vary substantially, the results of the Rotta trials may not be directly applicable in the U.S.²⁴⁷

A recently updated (searches through November 2004), good-quality Cochrane review included four short-term (4 to 8 weeks) head-to-head trials of glucosamine versus an oral NSAID (ibuprofen or piroxicam).²⁴⁸ Two of the trials were rated 5 out of 5 on the Jadad scale, and the other two were rated 3 or 4 out of 5. Rotta Research Laboratories sponsored three of the trials; the fourth²⁴⁹ was also conducted in Europe, but funding information was not reported. One of the trials has only been published as an abstract,²⁵⁰ and analyses were based on data from an unpublished manuscript. Two of the four trials found glucosamine superior to oral NSAIDs for efficacy,^{249, 250} and two found no difference.^{251, 252} In pooled analyses, glucosamine was superior to an oral NSAID for improving pain (three trials, standardized mean difference -0.40 , 95% CI -0.60 to -0.19), but not for improving function using the Lequesne Index (two trials, SMD -0.36 , 95% CI -1.07 to 0.35). Glucosamine was also associated with fewer adverse events (RR 0.29 , 95% CI 0.19 to 0.44) and withdrawals due to toxicity (RR 0.06 , 95% CI 0.01 to 0.25). Two small (N=40 and N=45), 12-week Canadian trials, neither funded by Rotta Research Laboratories, have also recently been published. Neither found differences between glucosamine and ibuprofen for general osteoarthritis pain²⁵³ or for temporomandibular joint osteoarthritis.²⁵⁴ Only limited details of the study design were reported for the first trial, though the second met all criteria for a good-quality study.

Evidence regarding the efficacy of glucosamine compared with placebo has also been mixed. The Cochrane review found glucosamine no better than placebo when the analysis was restricted to the eight trials with adequate allocation concealment.²⁴⁸ By contrast, when all placebo-

controlled trials were included in the analysis, glucosamine was superior for both pain and function using the Lequesne index. The benefits of glucosamine also varied substantially depending on the preparation being studied. Specifically, glucosamine performed better in the seven trials evaluating the Rotta preparation (a prescription formulation available in Europe) (SMD -1.31, 95% CI -1.99 to -0.64) compared with the eight trials using non-Rotta preparations (SMD -0.15, 95% CI -0.35 to 0.05). In fact, all of the five trials that found no benefit from glucosamine evaluated a non-Rotta brand of glucosamine and also had limited or no affiliation with a manufacturer of glucosamine. Older systematic reviews found glucosamine superior to placebo, but did not include several newer and higher quality trials that demonstrated no effect, and also noted important methodological flaws that could have exaggerated estimates of effect.^{255, 256} The Cochrane review²⁴⁸ and one other recent, good-quality systematic review²⁵⁷ included two trials (one fair-quality and one good-quality) that found glucosamine (Rotta brand) superior to placebo for reducing progression of knee joint space narrowing over 3 years (SMD 0.24, 95% CI 0.04 to 0.43²⁴⁸ and RR 0.46, 95% CI 0.28 to 0.73²⁵⁷). Other trials were too short in duration (mean 9 weeks) to assess joint space narrowing as an outcome. In all of the systematic reviews, rates of adverse events were no different between glucosamine and placebo.

We identified no trials comparing chondroitin sulfate to oral NSAIDs. Three systematic reviews evaluated the efficacy and safety of chondroitin compared with placebo. The most recent, fair-quality systematic review found indistinguishable efficacy for glucosamine and chondroitin and combined the results of the trials.²⁵⁶ When all trials were pooled, active treatment was associated with an increased likelihood of being a responder (RR 1.59, 95% CI 1.39 to 1.83) compared with placebo. The results of the chondroitin trials were not reported separately. The chondroitin trials also received lower quality ratings than the glucosamine trials, but the effects of quality scores on the findings were not evaluated. Assessment of the effects of quality on assessments of estimates of benefit are important because an earlier, good-quality systematic review found pooled effect sizes for pain relief substantially lower for chondroitin trials with quality scores below the median (effect size 1.7, 95% CI 0.7 to 2.7) compared with trials with quality scores above the median (ES 0.8, 95% CI 0.6 to 1.0).²⁵⁵ Smaller chondroitin trials also reported higher effects. The third systematic review was also rated fair quality because it did not evaluate the effects of study quality on results.²⁵⁸ It found chondroitin superior to placebo for pain and function, but longer and larger studies were needed. All three systematic reviews found chondroitin tolerated as well as placebo, with only mild adverse events.

Results of a large (N=1,583), NIH-funded, randomized trial (Glucosamine/chondroitin Arthritis Intervention Trial) comparing placebo, celecoxib, glucosamine, chondroitin, and glucosamine plus chondroitin were recently published (Table 27).²⁵⁹ Using pharmaceutical grade glucosamine hydrochloride (rather than the over-the-counter glucosamine sulfate commonly available in U.S. as supplements not regulated as pharmaceuticals by the FDA) and chondroitin under an investigational new drug application, the study randomized patients stratified according to baseline pain severity. It found no differences between glucosamine, chondroitin, or the combination relative to placebo among all patients for achieving a clinical response (>20% improvement in WOMAC Pain score after 24 weeks), though the combination was superior to placebo for achieving a clinical response in an analysis of a small (20% of enrollees) subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, p=0.002). There were no statistically significant differences between celecoxib and any of the other active treatment arms (glucosamine alone, chondroitin alone, or glucosamine plus chondroitin) or placebo and either glucosamine or chondroitin alone. The

authors postulated that lack of effect in the mild baseline pain group could have been due in part to floor effects. High placebo response rates were also observed. All of the interventions were well tolerated.

Table 27. Response rates in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)

Intervention	All patients	Moderate-severe baseline pain (WOMAC pain score 301-400 mm)	Mild baseline pain (WOMAC pain score 125-300)
Placebo	60.1%	54.3%	61.7%
Celecoxib	70.1% (p=0.008 vs. placebo)	69.4% (p=0.06 vs. placebo)	70.3% (p=0.04 vs. placebo)
Glucosamine	64.0% (p=0.30 vs. placebo)	65.7% (p=0.17 vs. placebo)	63.6% (p=0.67 vs. placebo)
Chondroitin	65.4% (p=0.17 vs. placebo)	61.4% (p=0.39 vs. placebo)	66.5% (p=0.27 vs. placebo)
Glucosamine + chondroitin	66.6% (p=0.09 vs. placebo)	79.2% (p=0.002 vs. placebo)	62.9% (p=0.80 vs. placebo)

Key Question 1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?

Duration of exposure and dose may have an influence on the benefits and harms associated with selective and non-selective NSAIDs, though data are limited and somewhat inconsistent. For rofecoxib, the VIGOR trial found that an increased risk of cardiovascular events appeared to become apparent only after 8 months of treatment.¹⁰⁶ Similarly, initial reports of the APPROVe trial appeared to show a duration-dependent effect, as the cardiovascular event rate curves for rofecoxib and placebo diverged only after about 18 months.¹³² However, a re-analysis that included originally censored events (occurring 14 days or more after discontinuation of study drug) suggests that the curves began to diverge after only 4 to 6 months, with no evidence of deviation from the proportional hazard over time.¹³³ The lack of an association with shorter duration of exposure in VIGOR could have been due in part to lack of power to detect differences due to small numbers of events. Supporting this hypothesis are two recent meta-analyses that found that risk of cardiovascular events with rofecoxib¹²⁴ or COX-2 inhibitors in general¹²⁹ did not vary according to duration of treatment. One of the meta-analyses also found that cardiovascular risk of rofecoxib did not vary according to dose.¹²⁴ However, the presence or absence of dose-dependent cardiovascular effects are difficult to analyze because 85% (84/98) of the events in patients allocated to rofecoxib in placebo-controlled trials occurred at a dose of 25 mg/day.¹²⁹

Observational data also suggests that increased cardiovascular risk with rofecoxib may occur at lower doses¹⁴⁵ and with shorter-term exposure.^{152, 261} Odds of acute MI were greater overall for rofecoxib relative to celecoxib in a case-control study of low-income Medicare beneficiaries

(mean age 79 years) exposed to treatment for ≤ 90 days.¹⁴⁵ The risk estimate for those taking rofecoxib > 25 mg (OR 1.70; 95% CI 1.07, 2.71) was greater than for those taking ≤ 25 mg (OR 1.21; 95% CI 1.01, 1.44), however.¹⁴⁵ Risk of CV events was similar for rofecoxib and meloxicam, regardless of duration, in a cohort study in which data was ascertained from an England National Health Services database using a Prescription Event Monitoring system.²⁶² In a case-control study of elderly patients in Quebec, the risk of acute myocardial infarction was highest following the first prescription of rofecoxib (adjusted RR 1.64, 95% CI 1.20 to 2.23 compared to non-use) and returned to baseline by the 8th prescription.²⁶¹

Some studies also suggest that duration of exposure and dose could influence the cardiovascular safety of celecoxib. Celecoxib was not associated with excess cardiovascular risk when compared with diclofenac or ibuprofen in the CLASS trials⁶⁰ or in meta-analyses^{105, 135} of mostly short-term trials of patients with arthritis. The long-term (33 months) APC polyp prevention trial was the first trial to clearly show an increased risk of cardiovascular events relative to placebo with celecoxib.¹⁰⁸ However, even though it's possible that the lack of an association in CLASS and earlier meta-analyses could be due in part to less risk with shorter duration of exposure, an alternative explanation is lack of power due to small numbers of events. Regarding dose-dependent effects, one recent meta-analysis¹²⁹ of 41 placebo-controlled trials found higher doses associated with greater cardiovascular risks relative to placebo ($p=0.03$), though most of the events at the highest dose (800 mg/day) came from two long-term polyp prevention trials.^{108, 263}

Analysis of the CLASS data also suggests that celecoxib was more effective at reducing GI events at 6 months compared with longer duration of exposure.⁶⁰ In fact, effects on pre-defined, serious GI complications were no longer present after 12 months, though interpretation of final results is problematic because of high withdrawal rates.⁹⁷ By contrast, in VIGOR, the GI benefit of rofecoxib compared to naproxen was seen early and sustained over the duration of the trial (median 9 months).¹⁹

One good-quality systematic review of eight trials found that higher doses of non-selective and partially selective NSAIDs were generally associated with greater efficacy for some measures of pain relief when directly compared to lower doses.²⁶⁴ Higher doses were also associated with greater withdrawals due to adverse events in two of four trials. In observational studies, the risk for GI bleeding with non-selective NSAIDs also appears to increase with higher doses.^{11, 191, 236} By contrast, the risk of bleeding associated with acetaminophen was not associated with dose in one meta-analysis of three case-control studies,²³⁶ though there was a modest dose response in another case-control study of elderly patients.²³⁵ At low over-the-counter doses, the risk of GI hospitalizations associated with aspirin, acetaminophen, and ibuprofen were similar to background rates in patients with rheumatoid arthritis or osteoarthritis in the ARAMIS database.²⁶⁵ A systematic review of observational studies found that use of aspirin and non-aspirin NSAIDs at over-the-counter doses is associated with an increased risk of GI bleeding, though the risk is lower than observed at prescription doses (approximately twofold greater risk at over-the-counter doses and sixfold or higher increases at heavy prescription levels.¹¹ One recent analysis of the Nurses' Health Study found that the risk of cardiovascular events was dose-related for both NSAIDs and acetaminophen.²³⁷

We found no studies evaluating the effects of alternative drug strategies such as intermittent dosing or drug holidays on risks and benefits of oral medication use. Although one difference between the APC trial (which found an increased risk of CV events with celecoxib) and the PreSAP trial (which reported no association) was twice-daily (APC) versus once-daily (PreSAP)

dosing, no study has directly compared such dosing strategies.¹⁰⁹ Furthermore, other studies of twice-daily dosing with celecoxib (such as CLASS⁶⁰ and ADAPT¹¹¹) reported no increase in CV risk.

Key Question 2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?

Demographic Subgroups Include Age, Sex, and Race

In general, the risk of cardiovascular, cardiorenal, and gastrointestinal adverse events associated with NSAIDs increase with age.¹³ In one UK population, for example, the risk of adverse gastrointestinal outcomes in patients taking selective or non-selective NSAIDs was 1.36 per 1,000 patient-years for all patients 25 years or older, but 4.03 per 1,000 patient-years in patients aged 65 or more.¹³⁸ Similarly, the risk of myocardial infarction was 1.71 per 100 person-years for all patients 25 years or older, but 4.57 per 100 person-years for those 65 or older.¹⁴⁶ We found no trial designed to assess whether the relative harms and benefits associated with different NSAIDs for osteoarthritis varies according to age. However, even if the relative benefits and harms associated with different drugs are consistent across age groups, the absolute effects would increase with age because of greater baseline CV and GI risk.

Studies that evaluated the efficacy and safety of selective and non-selective NSAIDs in average-risk elderly patients have generally reported similar findings compared with studies in populations with younger adults. An individual patient data meta-analysis of three celecoxib trials, for example, found effects of celecoxib 200 mg/day or 400 mg/day and naproxen 1,000 mg/day similar in elderly patients when evaluating WOMAC and SF-36 scores.²⁶⁶ For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on four of 10 components of the SF-36, while celecoxib 200 mg scored better on six, including general health. Celecoxib 200 mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study also confirmed that the overall incidence of GI adverse events was lower with celecoxib; the difference was about one event in 20 patients for celecoxib 200 mg and one in 10 for celecoxib 400 mg. Similarly, a meta-analysis of three rofecoxib trials reported similarly consistent efficacy for rofecoxib 12.5 mg or 25 mg daily compared to placebo among various subgroups defined by age, gender, race, location of osteoarthritis, baseline symptoms, and baseline functional status.²⁶⁷ Another meta-analysis found that trials of NSAIDs in patients over the age of 60 reported similar risks for GI complications compared to trials of patients under the age of 60.¹⁸³

Data suggesting differential effects of oral medications for osteoarthritis according to gender, ethnicity, or race are scant. In most of the published trials, a majority of subjects were women. As noted in the discussion of acetaminophen, results from the Nurses' Health Studies suggest that acetaminophen is associated with modest reductions in renal function in women,²⁴³ but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.²⁴⁶ The effects of different NSAIDs in specific ethnic minorities have only been evaluated in small studies. In a randomized crossover study of 25 black and

Hispanic patients on ACE inhibitors, peak increases in blood pressure were similar in patients on diclofenac compared with celecoxib.²⁶⁸ An observational study of 120 Native American patients seen in an Indian Health Service clinic in Phoenix who were switched to rofecoxib found that mean systolic blood pressure increased by 2.9 mm Hg overall ($p=0.015$) and by 4.8 mm Hg ($p=0.009$) in hypertensive patients.²⁶⁹ We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Co-Existing Diseases Include History of Previous Bleeding Ulcer Due to NSAIDs; Hypertension, Edema, Ischemic Heart Disease, and Heart Failure.

Rates of recurrent ulcer bleeding were similar for celecoxib 200 mg and the combinations of extended-release diclofenac 75 mg BID plus omeprazole 20 mg QD²⁷⁰ or naproxen 250 mg TID plus lansoprazole 30 mg QD²⁷¹ in two fair-quality, 24-week, parallel trials involving a total of 529 patients who presented with a bleeding ulcer (Table 28). There were also no differences between celecoxib and either combination therapy in other adverse events including GI, renal, and cardiovascular symptoms or in rates of withdrawals due to adverse events. One exception was that celecoxib 200 mg QD was associated with a higher rate of dyspepsia than naproxen 250 mg TID plus lansoprazole 30 mg QD.²⁷¹ The high rates of recurrent bleeding in both the celecoxib-treated patients and in the combination therapy groups—over 10 times as high as the rate in the CLASS trial— suggest that NSAIDs and coxibs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.

Table 28. Celecoxib in patients with bleeding ulcer history

Study Sample Size	Treatments	Recurrent ulcer bleeding at 6 months (difference; 95% CI)	Other adverse events	Withdrawals due to adverse events
Chan 2002 ²⁷⁰ n=287	Celecoxib 200 mg BID Diclofenac 75 mg BID plus omeprazole 20 mg QD	4.9% vs. 6.3% (-1.5%, CI -6.8, 3.8%; NS)	No differences	13.3% vs. 11.9%, NS*
Lai 2005 ²⁷¹ ** n=242	Celecoxib 200 mg QD Naproxen 250 mg TID plus lansoprazole 30 mg QD	3.7% vs. 6.3% (-2.6; CI -9.1, 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, $p=0.02$	10% vs. 7.4%, NS

*Includes withdrawals due to lack of efficacy

**Open trial

We found no randomized controlled trial evaluating the risk of bleeding with rofecoxib compared with celecoxib in high-risk patients. A Danish population-based case-control study of high-risk patients with previous gastrointestinal diseases found that rofecoxib (OR 2.1, 95% CI 1.2 to 3.5) and non-selective NSAIDs (OR 3.3, 95% CI 2.4 to 4.4), but not celecoxib (OR 1.3, 95% CI 0.7 to 2.8),²⁷² were associated with higher risks of upper gastrointestinal bleeding.

We found no randomized trials designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary according to underlying cardiovascular or renal risk. One recent analysis of three large polyp prevention trials of celecoxib or rofecoxib^{109, 132} and one observational study of rofecoxib²⁷³ found consistent risks for cardiovascular events among users at low and high baseline cardiovascular risk. However,

even if the relative risk of cardiovascular harms is consistent across risk groups, the absolute effects with any specific drug would be greater in patients at higher baseline risk. This is strikingly illustrated by a recent, good-quality population-based study of a very high risk group of 58,000 Danish patients with previous myocardial infarction that found hazard ratios for death of 2.80 (95% CI 2.41 to 3.25) for rofecoxib, 2.57 (95% CI 2.15 to 3.08) for celecoxib, 1.50 (95% CI 1.36 to 1.67) for ibuprofen, 2.40 (95% CI 2.09 to 2.80) for diclofenac, and 1.29 (95% CI 1.16 to 1.43) for other NSAIDs compared to non-use of NSAIDs.²⁷⁴ Because of high rates of death in this population (95 per 1000 person-years in those not using NSAIDs), the estimated number of patients needed to treat with an NSAID for one year to cause one additional death was very low, at 13 (95% CI 10-20) for rofecoxib, 14 (95% CI 10-24) for celecoxib, 45 (95% CI 29-102) for ibuprofen, and 24 (95% CI 16-45) for diclofenac.

Only a few trials have evaluated the effects of different medications on cardiovascular and cardiorenal events specifically in high-risk patients. Three randomized trials sponsored by the manufacturer of celecoxib found higher rates of hypertension or blood pressure increases in patients randomized to rofecoxib compared with patients randomized to celecoxib, but no differences in discontinuations due to adverse events or for episodes of heart failure.^{84, 85, 207} As noted earlier, the results of these trials must be interpreted cautiously because they evaluated possibly non-equivalent doses of rofecoxib and celecoxib, and because one of the trials⁸⁴ had important baseline differences suggesting inadequate randomization.

A meta-analysis funded by the manufacturer of rofecoxib found that in a high-risk subgroup of patients in whom aspirin was indicated (history of cardiovascular disease), rofecoxib was not associated with an increased risk of myocardial infarction compared with either placebo or non-selective NSAIDs.¹²³ However, the duration of the included trials may have been too short (median 3½ months) to detect an increased risk, few events were observed, and only a minority of patients received the high dose of rofecoxib evaluated in the VIGOR trial.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. A recent, good-quality population based retrospective cohort study, however, found that the risk of death and recurrent congestive heart failure was higher in patients prescribed NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) or rofecoxib (HR 1.27, 95% CI 1.09 to 1.49), each compared with those prescribed celecoxib.²¹¹ We also found no trials comparing the risks and benefits of different oral medications in patients with known renal failure.

Concomitant Anticoagulant or Aspirin Use

Concomitant anticoagulants. Concomitant use of anticoagulants and non-selective NSAIDs increases the risk of GI bleeding three- to six-fold compared to anticoagulants alone.^{275, 276} Several observational studies have evaluated whether COX-2 selective agents are associated with a lower risk for bleeding compared with non-selective agents in patients on anticoagulation.

A good-quality nested case-control study of elderly (>66 years old) patients on warfarin in Ontario, Canada, evaluated the association between hospitalization for upper gastrointestinal bleeding (361 cases) and use of selective or non-selective NSAIDs.²⁷⁷ It found that after adjustment for potential confounders (antiplatelet agents, hypoglycemic agents, glucocorticoids, gastroprotective agents, history of previous bleed, and comorbidities), recent use of non-selective NSAIDs (OR 1.9, 95% CI 1.4 to 3.7), celecoxib (1.7, 95% CI 1.2 to 3.6), and rofecoxib (2.4, 95% CI 1.7 to 3.6) were all associated with increased and overlapping risks for upper gastrointestinal bleeding, compared with non-use. Because this study relied on pharmaceutical

databases to identify exposures prior to hospitalization, it could not assess the confounding effects of over-the-counter use of aspirin, other NSAIDs, or acid suppressive medications. It also was unable to control for variations in INR level and the risk for bleeding.

A smaller, fair-quality nested case-control study of patients in the Netherlands evaluated the risk of bleeding in anticoagulated patients receiving partially selective (meloxicam or nabumetone) COX-2 inhibitors or non-selective NSAIDs.²⁷⁸ No case (N=154) received either celecoxib or rofecoxib. This study also differed from the Ontario study in that it included all cases of minor visible bleeding, hematoma, or black tarry stools. It used a questionnaire to assess exposure status and comorbidities. Patients were interviewed over the phone if answers were incomplete or unclear. The response rates were significantly higher in the cases (approximately 70%) compared with controls (approximately 31%). The study found that non-selective NSAIDs were associated with an increased risk of bleeding compared with partially selective NSAIDs after adjustment for duration of use and INR level (OR 3.07, 95% CI 1.18 to 8.03).

An open, crossover trial compared celecoxib 200 mg and rofecoxib 25 mg in 18 patients with OA, RA, or chronic pain who were stable (three consecutive INRs within 15% of each other) on warfarin therapy.²⁷⁹ The trial was designed to measure mean change in INR and safety parameters. Similar rates of edema, heart failure and other adverse events were found for celecoxib and rofecoxib. The INR increased by 5% to 15% between weeks one and three for both coxibs. Four minor bleeds were reported; none were associated with a significant decrease in hemoglobin concentration.

Postmarketing case reports of serious bleeding events, some fatal, have also been reported with concomitant anticoagulation and both rofecoxib and celecoxib. Most of these events occurred in elderly patients.^{135, 280}

We found no studies evaluating risks and benefits of concomitant anticoagulants and aspirin in patients with arthritis. Combination therapy has been studied in patients with indications for thromboembolic prophylaxis. However, the results of those studies are not directly applicable to patients with arthritis because of important differences in the populations (particularly with regard to cardiovascular risk), and because aspirin was used in lower, prophylactic doses (rather than anti-inflammatory and analgesic doses). One fair-quality meta-analysis (did not evaluate quality of included trials) found major bleeding risk increased with warfarin plus aspirin versus warfarin alone (at the same intensity) in patients with mechanical heart valves (3 trials, RR 1.58, 95% CI 1.02 to 2.44).²⁸¹ In patients with recent myocardial infarction or atrial fibrillation (one trial each), the increase in risk was not statistically significant (RR 3.07, 95% CI 0.33 to 28.38 and RR 2.13, 95% CI 0.20 to 23.03, respectively). In patients with mechanical heart valves, the increase in bleeding risk was offset by a reduction in thromboembolic events (RR 0.33, 95% CI 0.19 to 0.58), and there was no difference in all-cause mortality (RR 0.78, 95% CI 0.29 to 1.83). Other evidence on the risks and benefits of combination therapy has focused on comparing warfarin plus aspirin to aspirin alone. A recent good-quality meta-analysis of 10 trials, for example, found that the combination of warfarin plus aspirin increased the risk of major bleeding compared with aspirin alone following myocardial infarction or the acute coronary syndrome (RR 2.5, 95% CI 1.7 to 3.7).²⁸² However, the increase in bleeding risk was offset by lower risks for myocardial infarction, ischemic stroke, and revascularization. Mortality did not differ.

No study evaluated risk of bleeding in anticoagulated patients on acetaminophen compared with those on NSAIDs. A small, randomized controlled trial found acetaminophen associated with greater increases in INR levels compared with placebo.²⁸³ Several observational studies

have also found an association between excess anticoagulation and use of acetaminophen.^{284, 285} However, changes in INR are not the only important factor for predicting increased risk of bleeding. NSAIDs, for example, also affect platelet function and disrupt the gastric mucosal lining. Studies evaluating actual bleeding complications are necessary to better assess the comparative risks from acetaminophen and other NSAIDs.

No studies evaluated risk of bleeding in anticoagulated patients on glucosamine, chondroitin, or topical agents.

Concomitant aspirin. Beneficial effects of COX-2 selective inhibition on GI complication rates may be attenuated or eliminated by the concomitant use of aspirin. In the 20 per cent of patients in the CLASS trial who took aspirin in addition to their study drug, there was no difference in ulcer complications or ulcer complications plus symptomatic ulcers in patients randomized to celecoxib versus those randomized to diclofenac, ibuprofen, or the two NSAID comparators combined.⁹⁶ Similarly, a meta-analysis of randomized controlled trials found that beneficial effects of celecoxib on risk of endoscopically detected ulcers were reduced in patients on prophylactic aspirin (RR 0.49, 95% CI 0.28 to 0.86) compared with those not on aspirin (RR 0.27, 95% CI 0.16 to 0.48).⁶¹ This analysis excluded the results of the CLASS trials because they did not evaluate endoscopic ulcers as an outcome and because of high, differential withdrawal rates. A re-analysis that included the full CLASS trials results found no benefit (rather than a reduced benefit) from celecoxib in patients on aspirin (RR 0.96, 95% CI 0.63 to 1.46),²⁸⁶ but the appropriateness of combining data from trials reporting endoscopic ulcers with data from the CLASS trials on withdrawal rates, symptomatic ulcers, and ulcer complications, is disputed.²⁸⁷ Another meta-analysis found that use of aspirin increased the rate of endoscopic ulcers by about 6% in patients randomized to celecoxib (4.2% without aspirin and 9.9% with aspirin) and in those randomized to a non-selective NSAID (17.6% and 23.8%).⁶² In the TARGET trial, no reduction in ulcer complications with lumiracoxib compared to non-selective NSAIDs was observed in the subgroup of patients on aspirin (HR 0.79, 95% CI 0.40, 1.55).¹⁷⁵

There is less evidence on the effects of aspirin on the GI risk associated with rofecoxib. A recent trial that randomized osteoarthritis patients to placebo, enteric-coated aspirin (81 mg/day), rofecoxib 25 mg/day + aspirin 81 mg/day, or ibuprofen 2,400 mg/day found similar rates of endoscopic ulcers in the rofecoxib + aspirin arm (16.1%) and the ibuprofen alone arm (17.1%); both rates were significantly higher than the placebo (5.8%) and aspirin alone (7.3%) arms.²⁸⁸ A meta-analysis of aspirin users in two trials comparing celecoxib 200 mg daily and rofecoxib 25 mg daily found celecoxib associated with a lower rate of withdrawals due to GI adverse events than rofecoxib (0.7% vs. 3.9%, $p < 0.05$), as well as with GI symptoms.²⁸⁹ However, there were no reported serious GI events. Interpretation of these results is limited by nonequivalent dosing of the COX-2 inhibitors, pooling of data across trials, and post-hoc subgroup analyses of the aspirin-users data.

Concomitant aspirin use has not been shown to eliminate or reduce excess cardiovascular risks associated with COX-2 inhibitors. In large polyp prevention trials of rofecoxib¹³² and celecoxib,¹⁰⁹ use or non-use of low-dose aspirin did not affect the observed increased risk of thrombotic events.¹³² A recent meta-analysis of 84 placebo-controlled trials that permitted aspirin (including the polyp prevention trials) found a very similar risk of vascular events among those using aspirin (RR 1.57, 95% CI 0.90 to 2.72) and aspirin non-users (RR 1.51, 95% CI 1.14 to 2.01), though the absolute rate of events was higher in aspirin users (1.9%/year versus 1.1%/year).¹²⁹ Consistent with these findings, two large observational studies using the UK

GPRD¹⁸⁵ and QRESEARCH¹⁴⁶ databases found no significant interaction between concurrent NSAID and aspirin use and the risk of myocardial infarction. One observational study found that in patients with known cardiovascular disease, there was a higher rate of overall mortality (adjusted hazard ratio 1.93, 95% CI 1.30 to 2.87) and cardiovascular death among users of ibuprofen plus aspirin compared with users of aspirin alone, suggesting that ibuprofen (or other NSAIDs) could interfere with the cardioprotective effects of aspirin.²⁹⁰ However, this study only evaluated small numbers of patients on NSAIDs, and did not adjust for important comorbidities.

Key Question 3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Misoprostol, standard- and double-dose H2 blockers and PPIs were all effective in reducing the risk of NSAID-associated endoscopic gastric and duodenal ulcers relative to placebo in three good-quality systematic reviews (Table 29)²⁹¹⁻²⁹³ of numerous randomized controlled trials of OA/RA patients.^{9, 69, 291, 294-321} H2 blockers,³²⁰⁻³³⁰ misoprostol (RR 0.36, 95% CI 0.20 to 0.67), and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers, but not serious cardiovascular or renal illness or death.²⁹³

Misoprostol has been studied most extensively and is the only agent proven to decrease risk of ulcer complications (MUCOSA).³¹⁷ In a large, good-quality trial, misoprostol was associated with a rate of definite ulcer complications of 25/4404 (0.6%) compared to 44/4439 (0.9%) with placebo (p=0.049).³¹⁷ However, misoprostol is also the only agent to be associated with a significant risk of treatment withdrawal due to nausea (RR=1.30, 95% CI 1.08 to 1.55), diarrhea (RR=2.40, 95% CI: 2.05 to 2.81), and abdominal pain (RR=1.36, 95% CI 1.20 to 1.55).

Table 29. Placebo-controlled trials of gastroprotective agents²⁹¹⁻²⁹³

Treatment	# PCT studies Duration	Prevention of endoscopic ulcers		Prevention of clinical GI events*
		Gastric	Duodenal	
Misoprostol	1-1.5 months: 8 ≥ 3 months: 11	1-1.5 months: RR=0.17, 95% CI: 0.09 to 0.31 3 months: RR=0.26; 95% CI 0.17 to 0.39	1-1.5 months: RR=0.28; 95% CI 0.09-0.31 3 months: RR=0.47, 95% CI 0.33 to 0.69	Silverstein 1995 (MUCOSA): OR 0.598; 95% CI 0.364 to 0.982
H2 blockers	Standard doses (150 mg): 7 Double doses (300 mg): 3 1-3 months	Standard dose: insignificant effect Double dose: RR=0.44, 95% CI: 0.026 to 0.74	Standard dose at 1 and 3 months: RR=0.24, 95% CI: 0.10 to 0.57 and RR=0.36, 95% CI: 0.18 to 0.74 Double dose: 0.26, 95% CI 0.11 to 0.65	None
PPIs	4 Duration NR	RR=0.40, 95% CI 0.32 to 0.51	RR 0.19, 95% CI 0.09 to 0.37	None

*Upper GI hemorrhage, perforation, pyloric obstruction, death)

Table 30 reflects the results from five trials^{306, 309, 314, 319, 321} that directly compare one gastroprotective agent with another, as reported in the Canadian Coordinating Office for Health Technology Assessment review.²⁹² Both misoprostol and omeprazole were superior to ranitidine for the prevention of gastric ulcers. Omeprazole and lansoprazole also appeared superior to misoprostol and ranitidine for the prevention of duodenal ulcers.

Table 30. Head-to-head trials of gastroprotective agents²⁹²

Comparison	Reductions in ulcer risk	
	Gastric	Duodenal
Misoprostol vs. ranitidine* (2 trials; n=600)	RR=0.12 95% CI 0.03 to 0.89	No differences
Omeprazole 20 mg vs. ranitidine 150 mg (1 trial, n=425)	RR=0.32 95% CI 0.17 to 0.62	RR=0.11 95% CI 0.01 to 0.89
PPI** vs. misoprostol***	No differences	RR=0.29 95% CI 0.15 to 0.56

*standard dose

**omeprazole or lansoprazole

***secondary prophylaxis trials

A good-quality meta-analysis of 26 trials found co-administration of a PPI with a non-selective NSAID associated with a greater reduction in dyspepsia, epigastric pain and nausea than a selective COX-2 inhibitor alone, when each was compared to a non-selective NSAID alone (relative risk reduction 66% and absolute risk reduction 9% for the PPI + non-selective NSAID versus RRR 12% and ARR 3.7% with COX-2 inhibitor).³³¹

Key Question 4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?

Topical NSAIDs - Efficacy

Four trials directly compared topical and oral NSAIDs for osteoarthritis. Two recent good-quality systematic reviews^{332, 333} included three³³⁴⁻³³⁶ of these trials (an older systematic review was excluded because its results appear outdated.³³⁷). One systematic review (by Lin et al³³²) only included osteoarthritis trials, while the other systematic review (by Mason et al³³³) included osteoarthritis and other chronic pain conditions. The systematic reviews also used different methods for abstracting and pooling efficacy data. Specifically, the primary outcome in Mason et al was a dichotomous outcome: the proportion of patients with clinical success (defined as approximately a 50% reduction in pain) at the end of the trial. By contrast, the primary outcome used by Lin et al was continuous: the difference in standardized effect sizes for the outcomes of pain, function, or stiffness measured at the end of each week of treatment. Two^{335, 336} of the trials received 5 out of 5 points on the Jadad quality scale; the third³³⁴ received a score of 3.³³³ Mason et al found topical and oral NSAIDs equivalent for clinical success after 3 to 4 weeks

(pooled relative risk 1.1; 95% CI 0.9 to 1.3).³³³ Although Lin et al found topical NSAIDs inferior to oral NSAIDs for pain and function after one week of treatment, this finding was based on data from only one RCT (effect size -0.38 for pain, 95% CI -0.66 to -0.10 and ES -0.32 for function, 95% CI -0.60 to -0.04).³³² There were no significant differences between topical and oral NSAIDs after 2 (one RCT), 3 (two RCTs) or 4 (one RCT) weeks. Effect sizes could not be calculated for one of the three RCTs.³³⁴

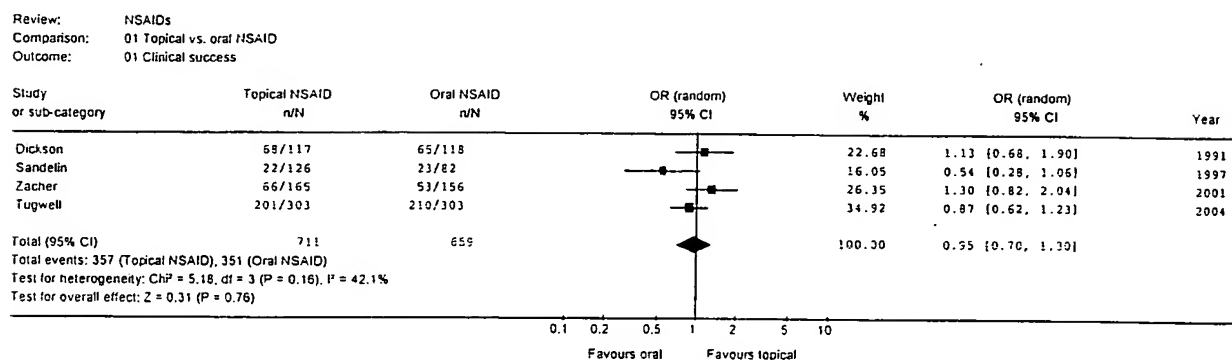
The largest and longest trial (by Tugwell et al) comparing topical and oral NSAIDs was published in 2004—too late to be included in the systematic reviews.³³⁸ This good-quality study found the proportion of responders (as defined by Outcomes Measures in Arthritis Clinical Trials and the Osteoarthritis Research Society VI recommendations) at 12 weeks similar in patients randomized to topical or oral diclofenac (66% vs. 70%, $p=0.37$). There were also no clinically relevant differences for the outcomes of mean change in pain scores, physical function, or patient global assessment. The topical diclofenac evaluated in this trial was a proprietary formulation with DMSO (a drug not approved for topical use in humans by the FDA) not available in the U.S.

We pooled rates of clinical response from the four trials (including Tugwell et al) comparing topical and oral NSAIDs, using intention-to-treat (missing values=failure) results and methods similar to the Mason meta-analysis. We found no differences between topical and oral NSAIDs (OR=0.95, 95% CI 0.70-1.30). It should be noted that the Sandelin study, which reported the lowest efficacy for topical versus oral NSAIDs, evaluated topical eltenac, a drug that is no longer being investigated for use in humans.³³⁵

Table 31. Head-to-head trials of topical versus oral NSAID for osteoarthritis

Author, year	Condition Number enrolled	Comparison	Duration of study	Definition of clinical success
Dickson, 1991 ³³⁴	OA of knee 235	Piroxicam 0.5% Ibuprofen 400 mg po tid	4 weeks	Patient global assessment 'good' or 'excellent'
Sandelin, 1997 ³³⁵	OA of knee 208	Eltenac 1% gel Diclofenac 50 mg bid	4 weeks	Physician global assessment 'good'
Zacher, 2001 ³³⁶	OA of fingers 321	Diclofenac 1% gel Ibuprofen 400 mg po tid	3 weeks	$\geq 40\%$ improvement in pain on 100 mm VAS
Tugwell, 2004 ³³⁸	OA of knee 622	Diclofenac 1.5% in carrier with 45.5% DMSO Diclofenac 50 mg po tid	12 weeks	OMERACT VI criteria ³⁸ for clinical responder

Figure 1. Clinical success in trials comparing a topical versus an oral NSAID



Only three small (sample sizes 40, 85, and 129), short-term (2- to 4-week) trials directly compared different topical NSAIDs for chronic pain conditions. They found no differences between topical diclofenac and indomethacin,³³⁹ topical flurbiprofen and pikeprofen,³⁴⁰ or topical ketoprofen and diclofenac.³⁴¹

The two systematic reviews came to somewhat different conclusions regarding the efficacy of topical NSAIDs compared with placebo. Lin et al found that topical NSAIDs were effective only during the first 2 weeks of treatment.³³² However, their conclusions at 3 and 4 weeks were entirely based on three trials that evaluated eltenac gel (no longer produced or studied for human use) or a topical salicylate (no longer classified as a topical NSAID). Mason et al, on the other hand, found NSAIDs superior to placebo (relative risk for improvement in symptoms 1.9, 95% CI 1.7 to 2.2) from 14 placebo-controlled trials of varying duration, with a number needed to treat for one case of clinical success (approximate 50% reduction in pain) of 4.6 (95% CI 3.8 to 5.9).³³³ Results were not sensitive to quality ratings, trial sample size, outcome measured, or condition (knee osteoarthritis versus other musculoskeletal conditions).

Four placebo-controlled trials of topical NSAIDs for osteoarthritis³⁴²⁻³⁴⁵ have been published since the systematic reviews were conducted. Three of these trials lasted longer than 4 weeks, and all found topical NSAIDs effective. The results of these trials are summarized in Table 32 for the dichotomous outcome “clinical success.” The longest trial of topical versus oral NSAIDs—a 2-year study of topical versus oral ibuprofen funded by the UK Health Technology Assessment Program—will not be completed until 2007.³⁴⁶

Table 32. Clinical success rates in recent placebo-controlled trials of topical NSAIDs

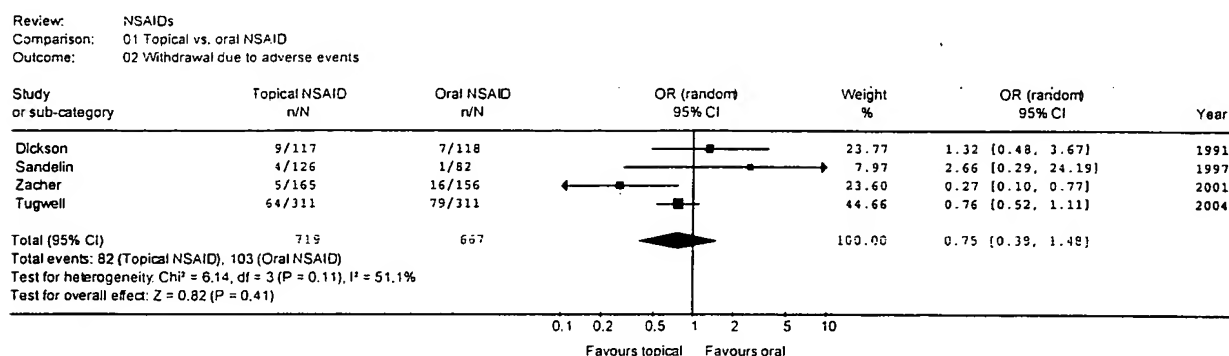
Study	Duration	Definition of 'clinical success'	Treatment group	Proportion of subjects classified as 'clinical success' at end of study period
Bookman, 2004 ³⁴³	4 weeks	>50% reduction in pain	Diclofenac Vehicle-control Placebo	44/84 (52.4%) 26/79 (32.9%) 28/84 (33.3%)
Roth, 2004 ³⁴⁴	12 weeks	>50% reduction in pain	Diclofenac Vehicle-control	79/163 (48.5%) 55/159 (34.6%)
Baer, 2005 ³⁴²	6 weeks	>50% reduction in pain	Diclofenac Vehicle-control	46/105 (43.8%) 27/107 (25.2%)
Trnavsky, 2004 ³⁴⁵	7 days	Reduction of >18 mm in VAS or >23% from baseline for pain	Ibuprofen Placebo	21/25 (84.0%) 10/25 (40.0%)

Placebo-controlled trials also suggest that topical NSAIDs differ with regard to efficacy. Topical diclofenac, which has been evaluated in the most (eight) trials, was consistently superior to placebo or associated with a trend towards superiority.^{333, 342-344} Several of these trials evaluated a proprietary compound (not available in the U.S.) of topical diclofenac in a carrier containing DMSO (Pennsaid®).³⁴⁷ Ibuprofen was superior to placebo for chronic pain conditions in three RCTs.^{333, 345} By contrast, evidence regarding the efficacy of other topical NSAIDs for chronic conditions is much more scant (see Mason,³³³ Additional Files 4 and 5). Four trials found topical piroxicam no better than placebo, homeopathic gel, or glyceryl trinitrate 1% cream. One RCT found topical ketoprofen no better than placebo. Topical felbinac, flufenamate, and indomethacin have only been evaluated in one or two small trials each. Evidence on topical flurbiprofen was mixed: one trial found topical flurbiprofen superior to placebo, but another found no differences.

Topical NSAIDs – Safety

Topical NSAIDs were associated with increased local adverse events (skin reactions such as rash, itch, and burning) compared with oral NSAIDs in two recent systematic reviews.^{332, 333} However, there were no differences for total adverse events, systemic adverse events, withdrawal due to adverse events, gastrointestinal events, or central nervous system events. For the outcome of withdrawal due to adverse events, we found no differences when we pooled the three trials included in the earlier reviews and a fourth,³³⁸ more recent trial.

Figure 2. Withdrawal due to adverse events in trials comparing a topical to an oral NSAID



Among the head-to-head trials, Tugwell et al provides the most information about adverse events because it has the largest sample size, the longest duration of follow-up, and used pre-specified definitions for adverse events and adverse-event severity.³³⁸ Topical diclofenac was associated with more local skin reactions but with fewer systemic and laboratory adverse events (Table 33).

Table 33. Adverse events from a trial comparing topical to oral diclofenac³³⁸

Adverse event	Topical diclofenac in DMSO carrier (n=311)	Oral diclofenac (n=311)	P value for difference
Withdrawal due to adverse event	21%	25%	0.15
Increase in mean blood pressure \geq 5 mm Hg	24%	28%	0.30
Dry skin	27%	1%	<0.0001
Rash	12%	2%	<0.0001
Pruritus	6%	0.6%	<0.0001
Gastrointestinal events (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, melena, nausea, vomiting)	35%	48%	0.0006
Severe gastrointestinal event (defined as producing significant impairment of functioning and definite hazard to patient's health)	2.6%	10.2%	0.0003
Melena	1%	2%	0.36
Asthma	3%	0.6%	0.02
Dizziness	0.6%	4%	0.002
Dyspnea	0%	2%	0.01
Hemoglobin went from normal to abnormal	2%	10%	<0.0001
Alanine transaminase increase to >3 times the upper limit or normal	1.1%	4.7%	0.01
Creatinine clearance went from normal to abnormal	4%	10%	0.01

No RCT was adequately designed to assess risks for serious but uncommon adverse events such as myocardial infarction, renal failure, or gastrointestinal bleeding. We identified one case-control study (1,103 cases) that evaluated the risk of hospital admission for upper gastrointestinal bleeding and perforation in patients taking topical NSAIDs.³⁴⁸ After adjusting for the confounding effects of exposure to oral NSAIDs and ulcer healing drugs, there was no association between exposure to topical NSAIDs within 45 days of an upper GI bleed (OR 1.45, 95% CI 0.84 to 2.50 with community controls and OR 1.06, 95% CI 0.60 to 1.88 with hospital controls). By contrast, oral NSAIDs were associated with increased risk (OR 2.59, 95% CI 2.12 to 3.16 for community controls and 2.00, 95% CI 1.60 to 2.50 for hospital controls). In a nested case-control study of the General Practice Research Database, topical NSAID use was not associated with symptomatic peptic ulcer (RR=1.0 versus non-use, 95% CI 0.6 to 1.7), though oral NSAID use was associated with increased risk (RR=4.0, 95% CI 3.2 to 5.1).²³⁴

We identified one case-control study of similar design that found exposure to topical NSAIDs not associated with acute renal failure (adjusted OR 1.33, 95% CI 0.79 to 2.24 using community controls and 1.04, 95% CI 0.60 to 1.83 using hospital controls).³⁴⁹ Recent exposure to oral NSAIDs, on the other hand, was associated with increased risk of renal failure using either community (adjusted OR 2.20, 95% CI 1.49 to 3.25) or hospital (adjusted OR 1.84, 95% CI 1.15 to 2.93) controls. We identified no studies comparing the risk of cardiovascular events in persons on topical versus oral NSAIDs.

Topical Salicylates (Including Capsaicin)

We identified no trials comparing topical salicylates to oral or topical NSAIDs. One recent good-quality systematic review found topical salicylates superior to placebo for pain relief when data from six trials were pooled (relative benefit 1.5, 95% CI 1.3 to 1.9; NNT 5.3, 95% CI 3.6 to

10.2).³² However, the three higher quality trials found no significant benefit (relative benefit 1.3, 95% CI 0.98 to 1.6). Local adverse events were rare, but the quality of adverse-event reporting was poor.

We identified no trials comparing topical capsaicin to oral or topical NSAIDs. One recent good-quality systematic review found that for chronic musculoskeletal pain, capsaicin was superior to placebo for achieving clinical success (defined as approximately a 50% reduction in pain), with a relative benefit of 1.5 (three trials, 95% CI 1.1 to 2.0) and number needed to treat of 8.1 (4.6 to 34).³⁵⁰ About 54% of patients had local adverse events with capsaicin, compared with 15% with placebo (relative risk 3.6, 95% CI 2.6 to 5.0). Withdrawals due to adverse events were also significantly more likely with capsaicin (13% vs. 3%, relative risk 4.0, 95% CI 2.3 to 6.8). An older systematic review was excluded because it appears outdated.³⁵¹

Chapter 4. Summary and Discussion

The table below summarizes the strength of evidence and results for each key question. Publication bias is an issue for all of these questions, because we do not know the complete details or results of unpublished trials submitted to the FDA or trials that have been conducted but not published or submitted to the FDA

Table 34. Summary of findings with strength of evidence

Key Question	Level of Evidence	Conclusion
1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?		
Efficacy: Non-selective NSAID vs. non-selective NSAID	Non-selective NSAID vs. non-selective NSAID: <i>good</i> . Consistent evidence from several good-quality systematic reviews and published trials. Salsalate vs. aspirin. <i>Poor</i> . One short-term trial. Salsalate or aspirin vs. non-aspirin NSAIDs. <i>Poor</i> .	No difference in efficacy between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac). No difference between salsalate and aspirin in one short-term trial. There were no trials or eligible observational studies of salsalate or aspirin vs. non-aspirin NSAIDs.
Efficacy: COX-2 selective vs. non-selective NSAID	Good. Consistent evidence from many published trials	No difference.
Efficacy: COX-2 selective vs. COX-2 selective	Good. Consistent evidence from six published trials.	No clinically significant differences at comparable doses.
GI and CV safety: Rofecoxib	Good. One large published trial, multiple meta-analyses and systematic reviews of published and unpublished trials, multiple observational studies.	In a pivotal, long-term trial (VIGOR) of patients with rheumatoid arthritis, rofecoxib 50 mg daily reduced symptomatic ulcers and serious ulcer complications compared with naproxen. After an average of 9 months, rofecoxib use was associated with 1 fewer symptomatic ulcer for every 62 patients treated; one fewer serious GI complication for every 191; and one additional MI for every 333 patients. The overall rate of serious adverse events, however, was higher with rofecoxib than naproxen. Higher-quality systematic reviews and observational studies are generally consistent with these findings (about 3.5 additional myocardial infarctions for every 1000 patients treated for one year). One long-term placebo-controlled polyp prevention trial also found an increased risk of MI.
GI and CV safety: Celecoxib	Fair: Multiple meta-analyses and systematic reviews of mostly short-term published and unpublished trials, multiple observational studies.	In the only published large, long-term study (CLASS), celecoxib was no better than diclofenac or ibuprofen for complicated or symptomatic ulcers at the end of follow-up. In subgroup analyses of patients not on aspirin, celecoxib was superior to ibuprofen but not to diclofenac for ulcer complications. There was no increase in the rate of cardiovascular events for celecoxib in CLASS. The overall rate of serious adverse events was similar

Key Question	Level of Evidence	Conclusion
		with celecoxib compared to ibuprofen and diclofenac. Systematic reviews and other meta-analyses of primarily short-term, unpublished data and lower doses found celecoxib superior to non-selective NSAIDs for ulcer complications. Observational studies are generally consistent with the short-term trials. However, recent meta-analyses found an increased risk of myocardial infarction with celecoxib compared with placebo (about 3.5 myocardial infarction for every 1000 patients treated for one year), with much of the evidence for increased risk coming from two large polyp prevention trials.
GI and CV safety: Valdecoxib	Fair: Fair quality meta-analyses of published and unpublished trials	Compared to non-selective NSAIDs, valdecoxib was associated with one fewer upper GI complication with valdecoxib for every 78 patients treated for 3 to 6 months. There was no association between valdecoxib and myocardial infarction in primarily short-term chronic pain trials. However, two short-term trials in a high-risk post-coronary artery surgery setting found that valdecoxib was associated with an acute two- to three-fold higher risk of cardiovascular events compared with placebo.
GI and CV safety: Etoricoxib	Fair: Several fair quality meta-analyses of published and unpublished trials	GI safety: Etoricoxib was associated with fewer perforations, symptomatic ulcers, and bleeds than diclofenac, ibuprofen, and naproxen (rate/100 patient-years 1.00 vs. 2.47). CV safety: Based on limited data from short-term trials, etoricoxib has a cardiovascular safety profile similar to non-selective NSAIDs, with the possible exception of naproxen.
GI and CV safety: Lumiracoxib	Fair: One large, long-term trial	GI safety: In patients not taking low-dose aspirin, lumiracoxib was associated with a lower risk of ulcer complications compared to naproxen and ibuprofen (1-year incidence 0.25% vs. 1.09%, $p < 0.0001$). CV safety: There were no differences in the risk of serious CV events (rates ranged from 0.11% to 0.38% after 1 year).
GI and CV safety: Partially selective NSAIDs	GI safety: Fair for meloxicam (short-term RCTs, meta-analyses, observational studies); poor for nabumetone and etodolac CV safety: Poor for all; two observational studies for meloxicam	GI safety: Meloxicam and non-selective NSAIDs were generally associated with similar risks of serious GI events; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac CV safety: Very sparse evidence that meloxicam and non-selective NSAIDs were associated with similar risks of serious CV events; no evidence for nabumetone and etodolac
GI and CV safety: Non-selective NSAIDs	Good for GI safety. Consistent evidence from many published trials, systematic reviews, and observational studies	No clear difference in GI safety between non-selective NSAIDs at commonly used doses. Naproxen was associated with a modest cardiovascular protective effect compared to other NSAIDs in a good-quality systematic

Key Question	Level of Evidence	Conclusion
	Fair for CV safety. No large, long-term controlled trials. Almost all evidence from observational studies	review of observational studies, but methodological issues could have affected the results. Comparative CV safety of other non-aspirin NSAIDs is not clear. A large systematic review of RCTs addressing this issue has not yet been published.
GI and CV safety: Aspirin	Fair. Many trials and systematic reviews, but almost exclusively in patients receiving aspirin at doses used for cardiovascular prophylaxis.	Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in prophylactic doses. There is insufficient evidence to assess safety of aspirin in doses used for pain control compared with non-aspirin NSAIDs.
GI and CV safety: Salsalate	Poor. Flawed observational data	Salsalate was associated with a lower risk of adverse events using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs. Almost no data is available on CV safety.
Mortality	Fair. Individual trials not large enough to detect differences in mortality. One meta-analysis of celecoxib using unpublished information, and one fair-quality observational study of non-selective NSAIDs.	No difference between celecoxib and non-selective NSAIDs, but few deaths occurred. In one cohort study, nabumetone was associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, edema, and impaired renal function	Fair. Multiple systematic reviews, clinical trials, and observational studies, but analyses limited by inconsistent reporting of results and probable publication bias	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. Indirect evidence and observational data suggests that rofecoxib is associated with a greater risk of hypertension, CHF, and edema compared to celecoxib. Rofecoxib was also associated with more cardiorenal events than celecoxib in three head-to-head trials of high-risk patients, but possible nonequivalent dosing limits interpretation of these results. No clear differences between celecoxib, partially selective, and non-selective NSAIDs.
Hepatotoxicity	Good. Systematic reviews of multiple trials and observational studies	Clinically significant hepatotoxicity was rare. Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. Among currently marketed NSAIDs, diclofenac was associated with a higher rate of liver-related discontinuations compared with placebo (2.17%).
Tolerability	Good for coxibs and non-selective NSAIDs (consistent results from multiple systematic reviews); fair for partially selective NSAIDs, aspirin, and salsalate (few meta-analyses and short-term trials)	Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were at least as well tolerated and aspirin was less tolerated; salsalate was less well tolerated than non-selective NSAIDs in 2 of 3 trials, but less toxic in flawed observational studies; no clear differences among coxibs or among non-selective NSAIDs
Acetaminophen	Good overall. Consistent results from multiple systematic reviews for efficacy and GI adverse events. Poor for cardiovascular safety	Acetaminophen is modestly inferior to NSAIDs for reducing pain and improving function. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies).

Key Question	Level of Evidence	Conclusion
	(no evidence on myocardial infarctions) and fair for renal safety (observational studies)	Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). Acetaminophen does not appear to be associated with an increased risk of hepatotoxicity at therapeutic doses in patients without underlying liver disease.
Glucosamine and chondroitin	Fair. Inconsistent evidence from clinical trials. The most promising results have been obtained in trials funded by a European manufacturer of pharmaceutical grade glucosamine not approved in the U.S.	A recent large, good-quality NIH-funded trial found that pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate alone or in combination were not superior to placebo among all patients studied. In a small subgroup of patients with at least moderate baseline pain, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. In older trials, many with some flaws, glucosamine was superior to oral NSAIDs and placebo in trials evaluating pharmaceutical grade glucosamine and funded by its manufacturer. Other trials found no difference between glucosamine and placebo or glucosamine and oral NSAIDs. Chondroitin was superior to placebo in older, flawed trials. Data on the effects of glucosamine on slowing progression of disease are limited to two trials showing beneficial effects on progression of knee joint narrowing. Glucosamine and chondroitin were consistently well tolerated, with no serious adverse events reported in the trials.
1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	Good for safety (consistent evidence from multiple clinical trials and observational studies), no evidence for alternative dosage strategies.	Risk of GI bleeding increases with higher doses of non-selective NSAIDs. Effects of dose and duration are somewhat inconsistent. Celecoxib was most effective for GI safety at 6 months and not after longer follow-up in the CLASS trials. A trend towards a dose-dependent CV risk of celecoxib was observed in a long-term prevention trial. CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial, but interpretation of earlier risk is imprecise because of small numbers of events. Most, but not all, observational studies suggest a dose-dependent effect of rofecoxib on MI risk.
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Good (age, sex) Poor (race)	Most studies included a majority of women. The risks of GI and CV events increase in older patients. The data that selective COX-2 inhibitors are safe and efficacious in different racial groups have been presented to the FDA. In the peer-reviewed literature, there is no evidence that the comparative efficacy of different selective and non-selective NSAIDs varies according to age, gender, or race.

Key Question	Level of Evidence	Conclusion
Pre-existing disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Previous bleeding: Good Hypertension, edema: Fair Ischemic Heart Disease: Poor (no comparative studies) Heart failure: Fair	Risk of bleeding is higher in patients with prior bleeding or PUD. Two trials found high rates of recurrent ulcer bleeding in patients randomized either to celecoxib or a non-selective NSAID + PPI. Risk of CV and renal events is higher in patients with cardiac and renal co-morbidities. In a single observational study that examined mortality, rofecoxib and non-selective NSAIDs were associated with higher rates of death and recurrent heart failure than celecoxib.
Concomitant anticoagulant use	Fair overall: Primarily observational studies	Concomitant use of anticoagulants and non-selective NSAIDs increase the risk of GI bleeding three- to six-fold. Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies, though there are case reports of serious bleeding events (primarily in the elderly). Warfarin plus aspirin (prophylactic doses) increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.
Concomitant aspirin use	Good for GI safety: Consistent evidence from clinical trials and observational studies Fair for CV safety: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on non-selective NSAIDs in one meta-analysis. In one trial, rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone (7%). Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or non-selective NSAIDs is limited, though three polyp prevention trials of rofecoxib or celecoxib found that concomitant aspirin use did not attenuate the observed increased risk of CV events.
3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Co-prescribing of misoprostol or PPIs with NSAIDs offers some advantages over full-dose H2-antagonists. PPIs are associated with the lowest rates of endoscopically detected <i>duodenal</i> ulcers. Misoprostol and PPIs are associated with similar rates of endoscopically detected <i>gastric</i> ulcers as PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of clinical GI events, it is also associated with an increased risk of GI-related adverse event withdrawals. Full-dose H2 blockers were associated with lower ulcer risk than placebo, but head-to-head trials against PPIs and misoprostol are lacking. Endoscopic duodenal ulcer risk for <i>standard</i> dose H2

Key Question	Level of Evidence	Conclusion
		blockers was lower than placebo; similar to misoprostol, and higher than omeprazole; standard dosages of H2 blockers and placebo were associated with similar gastric ulcer risk
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?		
Topical NSAIDs: efficacy	Good: Consistent evidence for selected topical NSAIDs from clinical trials	Topical NSAIDs are similar to oral NSAIDs for efficacy. Topical diclofenac is the best studied, though many trials evaluated a formulation using a DMSO carrier that is not available in the U.S. Topical ibuprofen was superior to placebo in several trials.
Topical NSAIDs: safety	Good: Consistent evidence from trials and systematic reviews and observational studies	Topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events are similar. Topical NSAIDs are superior for GI events, including severe events, and changes in hemoglobin (data from one good-quality trial).
Topical salicylates: (including capsaicin)	Fair: Only placebo-controlled trials, many of which were flawed	Topical salicylates were no better than placebo in higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

Discussion

This report provides a comprehensive summary of the comparative efficacy and safety of oral nonsteroidal anti-inflammatory drugs (NSAIDs) (selective, non-selective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease, though initial long-term trials of pharmaceutical grade glucosamine suggest an effect on radiologic evidence for disease progression.

Evidence regarding the benefits of oral NSAIDs from primarily short-term randomized controlled trials is abundant and demonstrates no clear, consistent differences for relieving pain or other osteoarthritis-related symptoms, or for superior tolerability. On the other hand, much of the uncertainty and confusion regarding NSAIDs centers on their comparative safety.

The trade-offs between reduced GI risk and increased CV harms was first clearly observed in VIGOR. In this trial, rofecoxib 50 mg daily significantly reduced symptomatic ulcers (NNT=62) and serious ulcer complications (NNT=191) compared with naproxen in patients with rheumatoid arthritis.¹⁹ However, the GI-protective effects were accompanied by a more than four-fold increase in myocardial infarctions, or one additional myocardial infarction for every 333 patients treated with rofecoxib. When considering all “serious” adverse events, moreover,

rofecoxib was not associated with any clear benefit compared with naproxen.¹¹⁴

Rofecoxib became the focus of intense scrutiny following publication of VIGOR. Subsequently, multiple observational studies^{138-141, 143-152} and systematic reviews^{124, 129} of RCTs have reported findings largely consistent with an increased risk of cardiovascular events with exposure to rofecoxib. Rofecoxib was voluntarily withdrawn from the market in 2004, after a long-term placebo-controlled polyp prevention trial reported increased cardiovascular risk.¹³² Valdecoxib was likewise voluntarily withdrawn from the market in 2005. Withdrawal was recommended by FDA based on their conclusion that valdecoxib associated with no clear GI benefit,¹¹⁷ an increased risk of serious skin reactions,¹⁶⁸ and potential increased risk of CV events.^{165, 166} As a result, celecoxib is the only selective NSAID currently available in the U.S.

The same concerns about the overall safety of rofecoxib have been directed at celecoxib. The evidence regarding the relative GI and CV safety of celecoxib, however, is less clear. In CLASS, the largest published study of GI complications, celecoxib was not significantly different than diclofenac or ibuprofen for either ulcer complications or myocardial infarctions by the end of follow-up.⁹⁴ Like the VIGOR trial, re-analysis of all serious adverse events in CLASS found no significant advantage for celecoxib.⁹⁴ On the other hand, systematic reviews and other meta-analyses of primarily short-term and frequently unpublished data found that celecoxib (primarily at lower doses than were used in CLASS) was associated with lower rates of ulcer complications than non-selective NSAIDs.^{62, 121} These findings, in combination with earlier systematic reviews of primarily short-term trials that found no increased cardiovascular risk with celecoxib, suggested a possible advantage of celecoxib over non-selective NSAIDs.^{62, 134, 135} More recent meta-analyses (including data from long-term polyp prevention trials) reporting an increased risk of myocardial infarctions with celecoxib (particularly at high doses) relative to placebo, however, raise additional questions about its appropriate use.^{129, 136}

Well-designed, long-term observational studies could provide 'real-world' information not available from most RCTs, which are usually designed as short-term efficacy trials that evaluate selected populations and employ rigid dosing regimens (often at high doses) under carefully controlled conditions. Observational studies are generally consistent with the RCTs in that celecoxib is consistently GI protective^{139, 162} or neutral¹³⁸ and not associated with higher risks of CV events relative to non-selective NSAIDs.^{144, 145, 150, 160} Additionally, celecoxib is associated with lower risks of serious GI events than rofecoxib.^{139, 142} Evidence from observational studies is less clear with regard to how celecoxib compares to rofecoxib in terms of CV risk due to differences in outcome reporting and in the number and type of factors adjusted for in outcome analyses.

An important drawback of the observational studies, however, is that they largely focus on individual adverse events in isolation. More informative analyses of the overall trade-off between risks and benefits would consider net harms from all serious adverse events. Our re-analysis of results from three studies^{139, 147, 163} reporting myocardial infarctions, heart failure hospitalizations, and gastrointestinal bleeding in an elderly Canadian population receiving multiple prescriptions suggests that in everyday use, celecoxib may confer net advantages in terms of the number of these events compared with rofecoxib and non-selective NSAIDs. However, additional studies on original data are needed to confirm this finding in other settings.

The cardiovascular effects of naproxen and other non-selective NSAIDs have been the subject of considerable debate since the publication of the VIGOR trial. At this time, among NSAIDs with sufficient evidence to assess cardiovascular risk, naproxen appears to offer the most favorable cardiovascular safety profile. In a recent, comprehensive systematic review,

naproxen (even at high doses) was moderately superior to COX-2 inhibitors for cardiovascular safety.¹²⁹ In addition, naproxen was the only NSAID (selective or non-selective) associated with a neutral cardiovascular effect relative to placebo, though these analyses were primarily based on indirect comparisons. The cardiovascular risks of non-naproxen, non-selective NSAIDs were similar to the selective COX-2 inhibitors, though most of the evidence was limited to high-dose ibuprofen and diclofenac. At this time, there is insufficient evidence to reliably judge the relative cardiovascular safety of other non-selective NSAIDs or the partially selective drugs nabumetone, diclofenac, and meloxicam. For GI safety, no clear advantage for any particular partially selective or non-selective NSAIDs has been demonstrated.

Topical NSAIDs may offer the advantages of local analgesic and anti-inflammatory effects without the systemic side effects of oral administration. They would probably be most useful in patients with a limited number of affected joints. Although topical NSAIDs appear comparable to oral NSAIDs for pain relief in several trials, the most convincing evidence comes from a recent trial that evaluated a proprietary formulation of diclofenac with DMSO that has not been FDA-approved.³³⁸ Topical NSAIDs appear safer than oral NSAIDs for GI safety, but data on comparative cardiovascular risks are not available. The relative benefits of topical rubefacients compared with topical or oral NSAIDs has not been adequately studied, and other than for capsaicin (which is sometimes classified separately from the rubefacients), there is insufficient evidence to prove that topical rubefacients are superior to placebo for osteoarthritis.

Acetaminophen is often considered an attractive alternative to NSAIDs because of its perceived safety profile. It was associated with GI-protective effects relative to non-selective NSAIDs,^{229, 231} though at the expense of modestly inferior efficacy.²³⁴ More evidence is needed to compare the effects of acetaminophen and NSAIDs on other important adverse events such as cardiovascular safety, renal dysfunction, blood pressure, and heart failure. However, one recent observational study found that heavy use of acetaminophen is associated with increased cardiovascular risks similar to that seen with NSAIDs.²³⁷ Aspirin is another alternative that has the advantage of a cardiovascular protective effect. However, nearly all of the evidence on cardiovascular and GI safety of aspirin is from trials using lower, preventative doses rather than higher anti-inflammatory and analgesic doses.

Glucosamine and chondroitin are widely available as over-the-counter supplements. The highly variable content of currently available products, however, remains a significant issue in the U.S. Further, nearly all of the trials demonstrating benefits of glucosamine have been conducted using pharmaceutical grade preparations not currently available in the U.S.²⁴⁸ Compared with the evidence for glucosamine, the evidence for chondroitin appears less promising. While these agents appear to be safe in the short term, high-quality, long-term safety data are sparse. A recent large, NIH-sponsored trial helps clarify the role of these supplements in management of osteoarthritis.²⁵⁹ It found that the combination of pharmaceutical grade glucosamine and chondroitin was modestly superior to placebo only in an analysis of a small subgroup of patients with at least moderate severity of baseline disease. Neither glucosamine nor chondroitin alone was superior to placebo overall or in the subgroup of patients with greater baseline severity. Data on effects of glucosamine on osteoarthritis progression are limited to two trials showing a beneficial effect on knee joint space narrowing over three years using a pharmaceutical grade preparation.

Strategies to reduce the risk of GI complications in patients taking NSAIDs include co-prescription of misoprostol, standard- or double-dose H2 blockers, or PPIs. All of these strategies are effective in reducing the risk of NSAID-associated *endoscopic* gastric and

duodenal ulcers relative to use of non-selective NSAIDs alone. Misoprostol (RR 0.36, 95% CI 0.20 to 0.67) and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers.²⁹³ Further, misoprostol is the only agent proven to decrease risk of clinical GI events, but is associated with an increased risk of withdrawals due to nausea, diarrhea, and/or abdominal pain.³¹⁷ In high-risk patients (those with a recent bleed), non-selective NSAIDs and the combination of a non-selective NSAID plus a PPI were both associated with similar, high rates of recurrent bleeding.^{270, 271}

In summary, each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. The role of selective and non-selective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report offers a clear overall advantage compared with the others, which is not surprising given the complex trade-offs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (cardiovascular, renal, GI, and others) involved. In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable trade-off for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and cardiovascular events), co-morbid conditions, and concomitant medication use (such as aspirin and anticoagulation). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant trade-offs.

Chapter 5. Future Research

- Nearly all of the clinical trials reviewed in this report were “efficacy” trials conducted in ideal settings and selected populations. “Pragmatic” trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- The cardiovascular safety of non-selective NSAIDs has not been adequately assessed in large, long-term clinical trials. Naproxen in particular may have a different cardiovascular safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials. The cardiovascular risks associated with the partially selective NSAIDs meloxicam, nabumetone, and diclofenac also have not been well studied.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall trade-offs between benefits and harms.
- The cardiovascular risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the cardiovascular risks have only occurred with prolonged use and at higher doses.
- Large, long-term trials of the GI and cardiovascular safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- Given the large number of patients who meet criteria for aspirin prophylaxis for cardiovascular events, more trials evaluating the effects of low-dose aspirin on GI and CV risks are needed.
- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.
- Genetic testing could theoretically help predict patients who are at higher risk of cardiovascular complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This is a promising area of future research.

- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing of certain COX-2 inhibitors could affect CV risk, this hypothesis has not yet been tested in a clinical trial.
- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the U.S. and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine. Additional long-term trials are also required to further evaluate effects of glucosamine on progression of joint space narrowing.
- No topical NSAIDs are FDA-approved in the U.S., yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO. A UK trial of topical versus oral ibuprofen is currently in progress and will help clarify the benefits and safety of topical versus oral NSAIDs. However, cohort studies using large observational databases may be required to adequately assess cardiovascular risk.

Addendum

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into our report, but their results generally appear consistent with our conclusions.

One meta-analysis evaluated risk of renal events (peripheral edema, hypertension, or renal dysfunction) and arrhythmias from 114 randomized trials of COX-2 selective NSAIDs [Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events. Meta-analysis of randomized trials. *JAMA*. 2006;296:(doi:10.1001/jama.296.13.jrv6001)]. It was rated fair-quality because it did not assess the quality of included studies. It found rofecoxib associated with increased risks of arrhythmia relative to control (placebo, other NSAID, or mixed/other) treatments (RR 2.90, 95% CI 1.07 to 7.88), though the number and rate of events was low (13/10126 or 0.1% in the rofecoxib arms, with 10 of the events ventricular fibrillation, cardiac arrest, or sudden cardiac death). The increase in risk was equivalent to about 1.1 additional arrhythmia events per 1000 patients treated with rofecoxib. Rofecoxib was also associated with an increased risk of peripheral edema (RR 1.43, 95% CI 1.23 to 1.66), hypertension (RR 1.55, 95% CI 1.29 to 1.85) and renal dysfunction (RR 2.31, 95% CI 1.05 to 5.07). For composite renal events (peripheral edema, hypertension, or renal dysfunction), risks were significantly higher with increased dose and increased duration of rofecoxib. Celecoxib was associated with lower risks of renal dysfunction (RR 0.61, 95% CI 0.40 to 0.94) and hypertension (RR 0.83, 95% CI 0.71 to 0.97) than control treatments, though there was no difference for composite renal events (RR 0.97, 95% CI 0.84 to 1.12) or arrhythmia (RR 0.84, 95% CI 0.45 to 1.57). There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and arrhythmia or renal events, though there was a trend towards increased renal events with valdecoxib/parecoxib (RR 1.24, 95% CI 1.00 to 1.55), and no arrhythmia events were reported in six trials of lumiracoxib.

Several factors complicate interpretation of estimates of arrhythmia risk from this meta-analysis. First, the rate of arrhythmias varied widely between control arms for different COX-2 selective inhibitors. For example, the rate of arrhythmias was fourteen-fold higher in the control arms of the celecoxib trials compared to the control arms of the rofecoxib trials (18/6568 or 0.3% vs. 2/10,126 or 0.01%). In addition, the proportion of specific arrhythmia events varied widely between drugs. For valdecoxib, over half (69/129 or 53%) of the arrhythmia events were atrial fibrillation, compared to 14% (3/22) for celecoxib and 8% (1/13) for rofecoxib. Finally, even though funnel plots and statistical tests did not suggest the presence of publication bias, only a minority of trials reported usable data on arrhythmia events. For example, only 10 of 37 included trials of celecoxib (accounting for about one-third of trial participants) had data that could be used in the analysis of arrhythmia events.

The second meta-analysis evaluated cardiovascular risk (primarily myocardial infarction) associated with NSAIDs from 23 observational studies (mostly of older populations) [McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296:(doi:10.1001/jama.292.13.jrv60011)]. Its results are largely consistent with our

qualitative assessment of cardiovascular risk from the observational literature. This meta-analysis appears to meet criteria for a good-quality systematic review, but its interpretation is complicated by the presence of substantial ($p \leq 0.001$), unexplained between-study heterogeneity for the main pooled analyses. It found rofecoxib associated with an increased risk of cardiovascular events at both lower (25 mg/day or less, RR 1.33, 95% CI 1.00 to 1.79) and higher (>25 mg/day, RR 2.19, 95% CI 1.64 to 2.91) doses, with the increased risk observable during the first month of treatment. Of the other NSAIDs, diclofenac (RR 1.40, 95% CI 1.16 to 1.70) was associated with the greatest cardiovascular risk, followed by indomethacin (RR 1.30, 95% CI 1.07 to 1.60) and meloxicam (RR 1.25, 95% CI 1.00 to 1.55). Celecoxib (RR 1.06, 95% CI 0.91 to 1.23), naproxen (RR 0.97, 95% CI 0.87 to 1.07), piroxicam (RR 1.06, 95% CI 0.70 to 1.59), and ibuprofen (RR 1.07, 95% CI 0.97 to 1.18) were not associated with increased risks. Only 3 of the 23 included studies reported adjusting for over-the-counter aspirin or NSAID use; two other studies included patients shortly after myocardial infarction that were all prescribed or presumed to be on aspirin.

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The Pain Market Outlook to 2011

By Melissa Zebrowski

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